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Editorial

What is a Normal Electrocardiogram?

THE ANSWER to the above question is not easy to give in a few words. Most cardiologists would probably define a normal tracing as one that shows normal sinus rhythm with no sinus tachycardia, bradycardia or other arrhythmia; in which the important intervals (P-R, QRS, and Q-T) are *normal;* and finally in which the size, direction, and form of the P waves, QRS complexes, and T waves are *normal.* If pushed further and asked what he means by normal in the above definition, the cardiologist would probably refer you to books, journals, or other published material in which criteria for deciding whether an electrocardiogram is normal may be found. If one were mean enough to ask how these criteria for normalcy were obtained, the cardiologist, after some reflection, would admit that they are largely experience factors, obtained by study of electrocardiographic findings in individuals with presumably normal hearts.

Since tables are available to decide whether the important intervals are of normal duration and the major waves of the electrocardiogram are of normal size, with some attention to the direction and form of the deflections, one might think it should be very simple to identify normal tracings. Greater familiarity with the problem and the many uncertainties involved make it clear that this is far from being true. As a concrete example, let us consider an electrocardiogram taken on an adult that appears normal but careful inspection of the R wave in lead II shows that it measures 20 mm. If the tracing is properly standardized (and this should always be checked) this corresponds to a voltage of 2.0 mv. The table for normal values in the *Electrocardiographic Test Book of the American Heart Association* gives a mean value of 7.1 mm. for R waves in lead II, with a range of variation of 1.8 mm. to 16.8 mm. A similar table to be found in the Fourth Edition of *A Primer of Electrocardiography* by Burch and Winsor gives a mean value of 11.5 mm. and a range of 4.0 mm. to 23.0 mm. for the R wave in lead II, and in another table prepared by Kossmann[1] one will find a mean value of 9.41 mm. and a range from 0.5 mm. to 28 mm. for the R wave in this lead. Thus, if we should follow the criteria for normalcy presented in the *Test Book of the American Heart Association,* it is clear that the electrocardiogram in question is "abnormal," while it would be normal (with respect to R in lead II) if either of the other tables is used. This is a confusing situation that could easily lead to bad interpretation of tracings, and it deserves further comment.

The reason for the wide differences in the normal range of the size of R in lead II in the three tables mentioned must be due largely to the fact that only 121 adults, with normal hearts, were used to obtain the data in the

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Test Book, while many more (475 in Kossmann's table) tracings from normal subjects were used in the other two. It is certain, as in any statistical study, that the larger the number of normal individuals included in an electrocardiographic survey, the greater the spread of any variate (like the size of R in lead II) will be. If adequate electrocardiographic data could be obtained on 10 million "normal" individuals in all age groups, we would have a better idea of the range of the "normal" electrocardiogram than is currently true. Such data are not, of course, available but, if they were, our troubles would not be over. How could one be sure that many of the variates close to the minimum or maximum values were not obtained from individuals with clinically unrecognized heart disease or with electrocardiographs that were not functioning properly? Uncertainties of this kind exist at the fringes of most distribution curves of groups of variates assembled to determine the range of normal of many different parameters. This is one reason why most electrocardiographers have not felt it worth while to do the tremendous amount of work involved in the statistical analysis of a very large group of "normal" electrocardiograms.

It may be mentioned in passing that in this issue of *Circulation* there is a short article describing an ingenious method for the visual display of a large mass of data relating to the size (and direction) of major waves in the normal electrocardiogram, written by Captain Paul S. Ezra while he was in military service in Korea. The figure in his paper is based on "normal" values given in the *Electrocardiographic Test Book of the American Heart Association*, but his technic could be used with any similar tables. Doctor Ezra should be complimented, not only on the clever visual method, but also on his full appreciation that his device is subject to all the limitations inherent in the tables. His "normal composite electrocardiogram" may be helpful in giving students and young physicians some idea of the variability of normal tracings, but it should not be used as a quick and easy method for identifcation of "normal" tracings by any physician responsible for their interpretation.

Although the above comments indicate that it may often be difficult to decide whether electrocardiograms should be classified as normal, the problem is even more complicated. If it is recalled that such records represent purely electrical phenomena associated with cardiac activity, may they not be "normal" in patients with heart disease and "abnormal" in the absence of organic heart disease of any kind? Unfortunately, the answer to both of the above alternatives is yes. In several of the electrolyte disturbances, especially involving abnormalities of serum potassium and calcium, the electrocardiogram may be grossly "abnormal" and subsequently return to normal in patients with entirely normal hearts. The other side of the coin is seen occasionally in patients with coronary artery disease, and two or more myocardial infarcts so located that the electrical abnormalities due to these lesions "neutralize each other," leading to a "normal" record. Furthermore, occasional patients with diffuse arteriosclerotic heart disease may show normal or nearly normal records, even though they are in or close to congestive heart failure.

The foregoing indicates clearly that physicians responsible for interpretation of electrocardiograms and those who use the electrocardiographic reports for diagnosis or management of their patients must understand that a report of "normal electrocardiogram" can only mean that the interpreter considers the record to satisfy accepted criteria for normality of the electrical record, but the physician responsible for the patient must use this information with full consideration of the history, physical examination, and other pertinent laboratory data. A policy of this kind for the use of all electrocardiographic reports, whether they are normal or abnormal, is strongly recommended by the writer.

Several reports in recent years by Davies,[2] Segall,[3] and Epstein and associates[4] have pointed out the variations in interpretation of the same group of normal or abnormal

electrocardiograms reported by several experienced electrocardiographers. This is disturbing, but perhaps even more upsetting is the fact that when some of the experts were asked to re-interpret the same tracings several months after the first readings were made, the reports were significantly different in a fair number of the records.

These differences in interpretation are clearly due to subjective factors and indicate that even the most experienced electrocardiographers are human beings and subject to the inconsistencies and biases that we all share. For some types of work, and this is particularly true of electrocardiographic surveys of large groups of individuals carried out by epidemiologists, these subjective influences are very undesirable, and for this reason Epstein and associates[4] suggest that electrocardiograms should be reported primarily in descriptive terms with inferences relative to diagnosis kept to a minimum. If such a course were generally followed, "electrocardiographic heart disease," due to unwarranted interpretation of nonspecific T-wave changes as indicating "coronary insufficiency" or the like, might decrease greatly. An experienced and conservative electrocardiographer is not likely, however, to include in his interpretation any diagnostic implications that are not justified by the objective findings in the tracings, and a purely descriptive report would not only be less valuable to the physician responsible for the patient but might lead to a very bad situation in which the only interpretation being attempted would be done by physicians with little background or experience.

The writer believes that, in ordinary clinical or hospital practice, there is a real need for electrocardiograms to be read and interpreted by the most experienced individual or group available to do this work, and that they should continue to report the tracings as "normal" or abnormal with any further comments that they feel may be justified.

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Discovery

We usually give the name of discovery to recognition of a new fact; but I think that the idea connected with the discovered fact is what really constitutes the discovery. Facts are neither great nor small in themselves. A great discovery is a fact whose appearance in science gives rise to shining ideas, whose light dispels many obscurities and shows us new paths. There are other facts which, though new, teach us but little; they are therefore small discoveries. Finally, there are new facts which, though well observed, teach nothing to anyone; they remain, for the moment, detached and sterile in science; they are what we may call raw facts or crude facts.

Discovery, then, is a new idea emerging in connection with a fact found by chance or otherwise.—CLAUDE BERNARD. *An Introduction to the Study of Experimental Medicine.* New York, The MacMillan Company, 1927, p. 34.

The Normal Composite Electrocardiogram

By PAUL S. EZRA, Capt. (MC)

NEWMAN recently has had this to say about the interpretation of the scalar electrocardiogram: ". . . (part) of the process involves quite a remarkable mental accomplishment. It involves an estimate of the magnitude and direction of the QRS deflections relative to that of the T waves, and then a comparison of the estimates with normal experience."[1]

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It is familiarization with the normal that is perhaps the most difficult task in electrocardiography. We have found a composite electrocardiogram (fig. 1) useful in this regard. It is made from the range of normal values to be found in the appendix of the American Heart Association's *Electrocardiographic Test Book*.[2] As can be seen, the normal ranges of the P, Q, R, S, and T deflections are depicted. The range of normality of S-T elevation is also shown. In the interest of simplicity, the various time intervals and the intrinsicoid deflection have not been included.

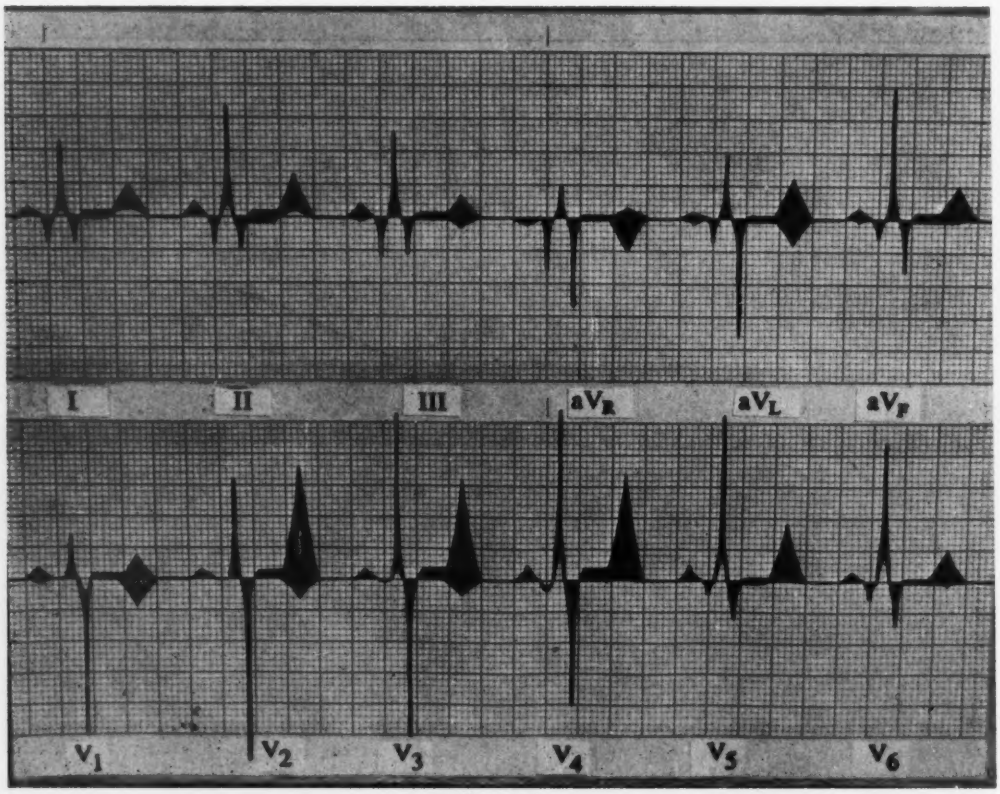

Figure 1

The normal composite electrocardiogram.

Even a casual study of the composite electrocardiogram recalls some of the classical empirical electrocardiographic observations: a flat or inverted T in lead I or II is not normal; the normal range of S-T elevation in the middle chest leads and lead II is quite labile; an inverted T in lead III is not necessarily pathologic, especially as an isolated finding, etc.

Such composite electrocardiograms might prove useful in pediatric cardiology, where the amount of any individual experience with specific ages is less than in the broad age spectrum of adult cardiology.

The same word of caution found in the preface to the *Electrocardiographic Test Book*[2] concerning the size of the sample from which some of the ranges were drawn also applies, of course, to the composite electrocardiogram. Also, certain combinations of borderline values probably do not occur except pathologically. For instance, the range of values for the heart's electric axis as calculated from the extremes of the QRS complexes in leads I and III of the composite electrocardiogram is −3 to 107 degrees, whereas the range of normality given by Jackson and Winsor[3] is −30 to 102 degrees.

With awareness of the limitations of the composite electrocardiogram it has been found to be a useful tool in the understanding of electrocardiography.

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The Early History of Instrumental Precision in Medicine

An astronomer gave us the first rude thermometer, and it seems to have been another, Herman Kepler, who first, and certainly before 1600, counted the human pulse, or at least left a record of having done this memorable thing. The publications in which he mentions the pulse date from 1604 to 1618. Does it not seem incredible that of the numberless physicians who sat by bedsides, thoughtful, with fingers laid upon that bounding artery, none should have had the idea of counting it? I quote in English what Kepler says. This great but fanciful man seems to have believed the pulse to have some relation to the heavenly motions, and used the time of the pulse in connection with arguments in favor of the Copernican system of astronomy. He says: "In a healthy man, robust and of full age, in one of melancholic complexion, or in a feeble man, generally for each second there is a pulsation of the artery, with no discrimination between systole and diastole; thus there should be in one minute sixty pulsations, but this slowness is rare, commonly 70 may be counted, and in the full-blooded and in women 80, four to each three seconds. Briefly, in one hour 4,000, more or less." The clock with which Kepler counted the pulse must have been such a "balance" clock as his master Tycho Brahe used.—S. Weir Mitchell, M.D. *Transactions of the Congress of American Physicians and Surgeons,* Second Triennial Session held at Washington, D.C., 1891. New Haven, The Congress, 1892, p. 173.

Variant Hemodynamic Patterns in Mitral Stenosis

By G. H. CARMAN, M.D., AND R. L. LANGE, M.D.

WHEN INDIVIDUALS with significant rheumatic mitral stenosis are studied by means of right and left heart catheterization, they show certain abnormalities of cardiovascular dynamics. At rest these patients usually demonstrate elevation of the left atrial, pulmonary wedge and pulmonary artery pressures, or, more frequently, a low cardiac index and normal or increased pulmonary arteriolar resistance.[1] With exercise, these vascular pressures increase further, and cardiac output becomes subnormal for the level of activity.[2]

Of 84 patients with predominant rheumatic mitral stenosis studied in this laboratory 11 showed hemodynamic findings which, though abnormal, differed from the usual patterns just described. Surprisingly, there was little, if any, clinical evidence suggesting an aberrant pattern. The purpose of this report is to present data from these patients and to consider the possible mechanism for these somewhat unusual responses.

Material and Methods

The histories, pertinent physical findings, electrocardiographic, and roentgenologic data are summarized in tables 1 and 2. Each patient underwent mitral commissurotomy. At operation the surgeon reported significant stenosis of the mitral valve in each case. The mitral valve orifices were described as being completely occluded by the tip of the index finger or measuring less than 1 cm.^{2} in greatest diameter. No significant degree of mitral incompetence was suspected or found. Postoperatively, all patients have claimed significant relief from symptoms.

Hemodynamic studies were made in the morning with the patient supine and fasting. Each patient was given 100 mg. of secobarbital sodium orally 30 minutes before the study. Right heart catheterization was performed via an exposed antecubital vein with a no. 6- or 7-French plain-tip woven Nylon cardiac catheter. A radial or brachial artery was cannulated percutaneously with a short bevel, no. 18- or no. 20-gauge needle. Pressures were recorded by a Waters photokymograph* from Heiland mirror galvanometers directly coupled to optimally damped Statham P23D strain-gage pressure transducers. Zero pressure reference level was one half of the anteroposterior chest diameter at the level of the second chondrosternal junction.[3] Cardiac outputs were measured by the direct Fick principle with a 3-minute collection of expired respiratory gases in a 120-liter Tissot spirometer. Blood from the pulmonary artery and the systemic artery was sampled simultaneously midway through the gas collection. Oxygen content of blood sampled was determined in duplicate by the technic of Van Slyke and Neill.[4] Analysis of oxygen and carbon dioxide content of expired gas samples was performed with the micro-Scholander method.[5]

After two resting measurements, the catheter tip was advanced to a distal branch of the pulmonary artery until the pressure curve associated with the pulmonary artery was no longer seen, and arterialized blood was obtained through the catheter. Mild exercise was started after resting values were recorded. The subjects exercised in the supine position by pedaling a stationary exercycle. After a minimum of 4 minutes of exercise cardiac output was again measured. (During the exercise determination, the catheter tip was withdrawn so as to lie freely in a branch of the pulmonary artery to allow successive measurements of pulmonary "capillary" or "wedge" and pulmonary artery pressure and the derivation of pulmonary arteriolar resistance.)

Mean pressures were determined by polar planimetry. The oxygen consumption per square meter of body surface area was used as the index, and arteriovenous oxygen difference for various levels of exercise oxygen consumption was obtained from published graphs.[6-8]

To evaluate changes in pulmonary wedge and pulmonary artery pressures, it was necessary to assume that intraalveolar and intrathoracic pres-

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*The Waters Corporation, Rochester, Minnesota.

Table 1

Clinical Characteristics of Patients with Variant Patterns in Mitral Stenosis

	Patient	Age	Sex	Orthopnea	Paroxysmal nocturnal dyspnea	Frank pulmonary edema	Hemoptysis	Exertional dyspnea	Fatigue	Peripheral edema	Systemic emboli
Group A											
	MJ	21	F	−	−	−	−	+	+	−	−
	FP	42	M	+	−	−	−	+	+	+	−
	CB	40	M	−	−	−	−	+	+	−	+
	RM	31	F	+	−	−	+	+	+	−	−
Group B											
	VL	18	F	+	+	−	−	+	+	−	−
	LC	31	F	+	+	+	−	+	+	−	−
	BH	20	F	+	+	+	+	+	−	−	−
	LR	28	F	+	+	+	−	+	−	−	−
	CJ	30	F	+	+	−	−	+	+	−	−
	LH	45	F	+	+	−	−	+	+	+	+
	EM	39	F	+	+	−	−	+	−	−	−

Table 2

Physical Signs and Electrocardiographic and X-ray Findings

	Physical findings					Electrocardiogram					Cardiac fluoroscopy		
											Enlargement of		
Pt.	Loud M_1	Loud P_2	Opening snap	Apical diastolic rumble	Other murmur	Rhythm	Axis QRS	LAH	RVH	LVH	LA	RV	LV
MJ	+	−	+	+	Dias. LSE	NSR	N	+	−	−	+	−	−
FP	+	+	+	+	−	AF	N	..	−	−	+	−	−
CB	+	+	+	+	−	AF	R	..	+	−	+	−	−
RM	−	−	+	+	Apical systolic	NSR	N	+	−	−	+	−	−
VL	+	+	+	+	−	NSR	N	+	−	−	+	±	−
LC†	+	+	+	+	−	NSR	N	+	−	−	+	−	−
BH†	+	+	+	+*	−	NSR	N	+	−	−	+	−	−
LR	+	+	−	+*	Dias. LSE								
CJ	+	+	+	+	−	NSR	R	+	−	−	+	−	−
LH	+	+	+	+	Apical systolic	AF	N	..	−	−	+	+	−
EM	+	+	+	+	−	NSR	N	+	−	−	+	−	−

*With diastolic thrill.

†Early pregnancy (8 to 10 weeks)

Abbreviations: LSE, left sternal edge; NSR, normal sinus rhythm; AF, atrial fibrillation; N, normal; R, right; LAH, left atrial hypertrophy; RVH, right ventricular hypertrophy; LVH, left ventricular hypertrophy; LA, left atrium; RV, right ventricle; LV, left ventricle.

sures did not vary significantly. Changes in the intravascular pressures were therefore considered to approximate changes in transmural pressure.

Results

Data from hemodynamic studies at rest and mild exercise are presented in table 3. The patients have been grouped into two general categories. Those in group A had normal pulmonary wedge and pulmonary artery pressures and low cardiac and stroke indices at rest. The patients of group B had elevation of pulmonary wedge and pulmonary artery pressures and normal cardiac and stroke indices at rest and during exercise.

The four patients in the first category, in addition, showed abnormally wide resting arteriovenous oxygen differences although the resting minute oxygen uptake was normal

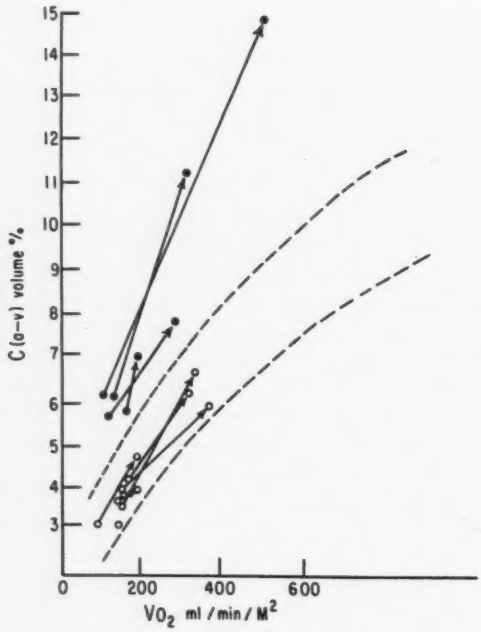

Figure 1

The arteriovenous oxygen difference during resting and exercise plotted against the $VO_2/M.^2$ in the patients studied. Group A deviated from the 95 per cent confidence limits for normal subjects both at rest and even more so during exercise.[7] In group B, however, the values were all within the limits of normal. Closed and open circles indicate A or B respectively.

(fig. 1). Despite the subnormal rise of cardiac index with exercise, the pulmonary wedge and pulmonary artery pressures did rise.

Patient C.B. was studied by cardiac catheterization on two occasions over a 3½-year period (table 4). During the first study, resting hemodynamic data were not outside normal limits although exercise was accompanied by an abnormal elevation of pulmonary artery pressure. At the time of the second study no change in heart size, electrocardiogram, or physical findings was evident. Nonetheless, in the intervening period the degree of mitral valve obstruction had become more severe and there was an increase in the severity of related symptoms. At the time of the second study, this more marked obstructive element was accompanied by a low resting cardiac output, primarily reflected by an increase in the resting arteriovenous oxygen difference. No perceptible change from the previous test could be detected in the resting values of left atrial, pulmonary wedge, or pulmonary artery pressures. An increase in cardiac output was still found during exercise.

Changes in the values of pulmonary arteriolar resistance associated with exercise are given for both groups in table 3. All 11 showed resting values for this derived parameter within or close to the upper limits of the normal range. In patients of category A, exercise was accompanied by an increase in pulmonary arteriolar resistance in two and a slight decrease in one. In group B, the pulmonary arteriolar resistance fell in three and increased in two.

Discussion

The measurable disturbances in the circulatory dynamics of patients with significant mitral stenosis can be considered to result primarily from the mechanical effects of valvular obstruction and secondarily from one or more mechanisms available to the heart and circulation in response to the obstruction. The mechanical effect is usually reflected by elevation of intravascular pressures proximal to the obstruction. Other compensatory mechanisms are less clear-cut, but it is attractive to theorize that a decrease of the effectiveness of myocardial contraction (and decreased stroke volume) into an increased pressure (pulmonary artery) would result in a lowered cardiac output, if rate is unchanged. A rise in pulmonary arteriolar resistance during exercise would also tend to limit flow and would become an additive factor.

Wood[1] considered elevation of pressures proximal to the mitral valve to be the first result of significant obstruction. Cardiac output then decreases as the consequence of limiting maximal pulmonary wedge or left atrial pressure imposed by the degree of stenosis. An increase in pulmonary arteriolar resistance usually accompanies sustained elevation of left atrial pressures and frequently continues to increase further. Because low blood flow and an increased resistance in the pulmonary arteriole would reduce the likelihood

Table 3

Hemodynamic Data at Rest (R) and Exercise (X) in Groups A and B

Pt.	State	BSA* ($M.^2$)	VO_2†	Arterio-venous oxygen difference (vol. %)	Q‡	Rate	Stroke index (ml./stroke/$M.^2$)	PC§ pressure	PA§ pressure	PAR‖
	Group A									
MJ	R	1.48	116	5.6	2.1	62	33	8	12	1.9
	X		243	7.6	3.2	88	36	12	16	1.3
FP	R	1.68	137	6.2	2.0	60	25	10	19	4.5
	X		331	11.3	2.9	100	29	23	38	5.2
CB	R	1.74	100	6.1	1.6	72	22	11	15	2.5
	X		516	14.8	3.5	132	26	30	55	7.6
RM	R	1.46	151	5.7	2.6	65	40	13	20	2.7
	X		199	6.9	2.9	70	41	..	26	..
	Group B									
VL	R	1.62	130	3.5	3.7	75	49	16	25	2.4
	X		337	6.6	5.1	105	49	25	41	3.1
LC	R	1.66	148	4.3	3.4	95	35	20	27	2.1
	X		297	5.9	5.1	116		30	36	1.0
BH	R	1.60	138	3.9	3.5	80	43	20	27	2.0
	X		362	5.8	6.3	126	50	42	48	1.0
LR	R	1.44	153	3.8	4.0	80	43	20	27	2.0
	..	...	...	..	..	..	..	..	..	..
CJ	R	1.75	131	3.5	3.7	100	37	22	29	1.9
	X		180	3.9	4.6	112	40	31	35	0.9
LH	R	1.76	95	3.0	3.2	72	44	26	36	3.1
	X		189	4.5	4.2	140	30	35	58	5.5
LM	R	1.70	131	2.8	4.7	90	52	16	39	4.7
			...	..	..	..	..	..	..	..

*BSA (Body surface area).

†VO_2, minute oxygen consumption is given in ml./min./M^2.

‡Q is flow in liters per minute per M^2.

§Pulmonary wedge and pulmonary artery pressure, mean values, in mm. Hg.

‖PAR, pulmonary arteriolar resistance (PA-PC)/cardiac index; (normal resting 1.8-4.5).

of pulmonary edema, Wood regarded this chain of events as "compensatory." On the other hand, Likoff[9] has suggested that mitral valve narrowing and the consequent rise in "filling gradient" would result initially in decreased cardiac output. With time, left atrial, pulmonary wedge, and pulmonary artery pressures rise progressively, cardiac output decreases further, and pulmonary arteriolar resistance increases.

A review of published hemodynamic data from significant mitral stenosis proved by operation or autopsy has disclosed cases similar to those described in this report.[10-12] The frequency of such cases is indicated in table 5. While the great majority (82 per cent) showed high pulmonary wedge and pulmonary artery pressures with low cardiac indices at rest, 5 per cent were similar to group A and 13 per cent resembled group B.

The chest x-rays and electrocardiograms shown in figures 2 and 3 are representative of patients of the two groups. Figure 2, obtained from M.J. of group A, shows the typical x-ray findings of pure mitral stenosis with no suggestion of ventricular enlargement. The accompanying electrocardiogram has the expected P-wave abnormalities. Figure 3 is from B.H. of group B. With the possible exception of a more prominent main pulmonary artery segment, both the x-ray and the electrocardiogram closely resemble those in figure 2. Despite nearly identical x-ray and electrocardiographic findings, as well as a similar de-

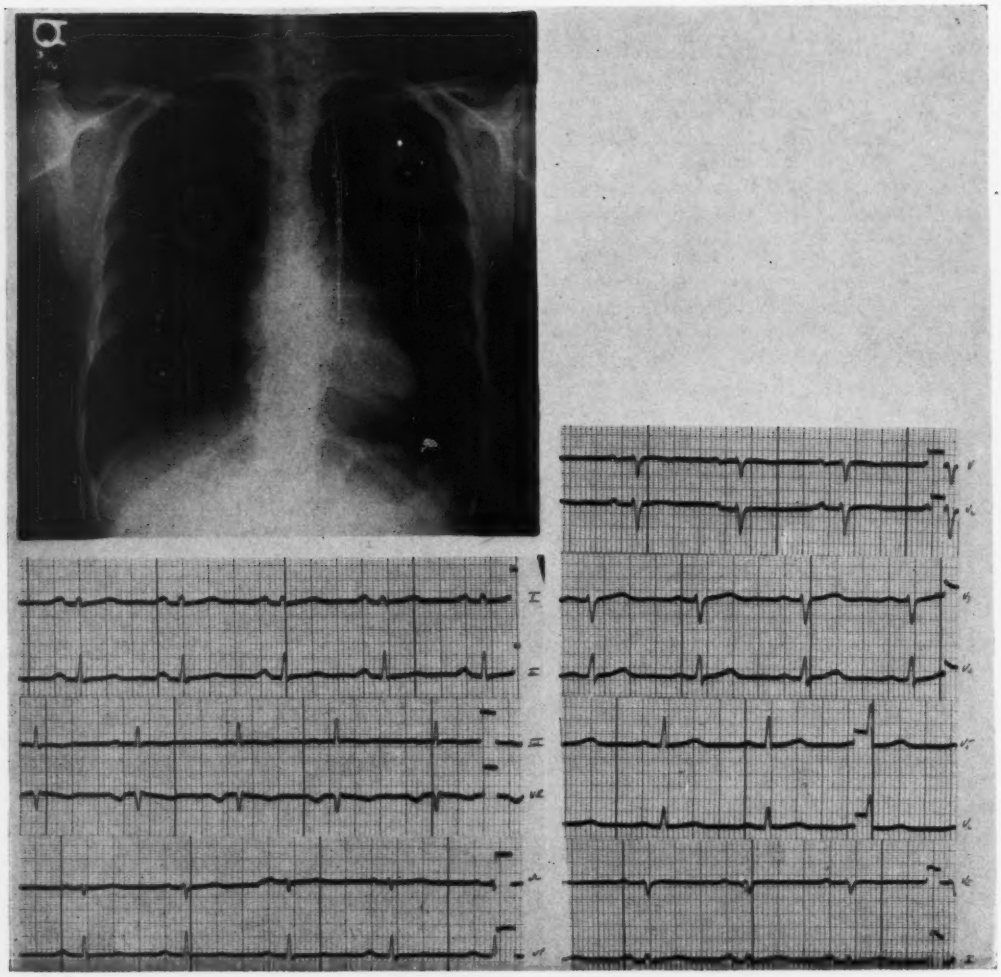

Figure 2

Posteroanterior chest x-ray and 12-lead (plus ensiform) electrocardiogram from patient M.J. of group A. Straightening of the heart border is seen but there is no increase in heart size. Except for P-wave abnormalities, the electrocardiogram is within normal limits.

gree of anatomic mitral valve obstruction, the hemodynamic patterns were widely different (table 3). Although the two groups showed no recognizable differenee in physical findings, electrocardiograms, or x-rays, the first group (low output, normal pressures) did not have paroxysmal nocturnal dyspnea or pulmonary edema (tables 1 and 2).

None of the patients in group A had elevated right ventricular diastolic pressures, roentgenologic evidence of ventricular enlargement, or electrocardiographic evidence of altered ventricular excitation or recovery (figs. 2 and 3, and tables 1 and 2). We believe that this supports the contention that such low flow values in these individuals are not the result of primary ventricular malfunction ("myocardial factor") but rather represent a readjustment of cardiac output to lower operating levels in response to unidentified factors. That certain patients with "tight" mitral stenosis may have normal

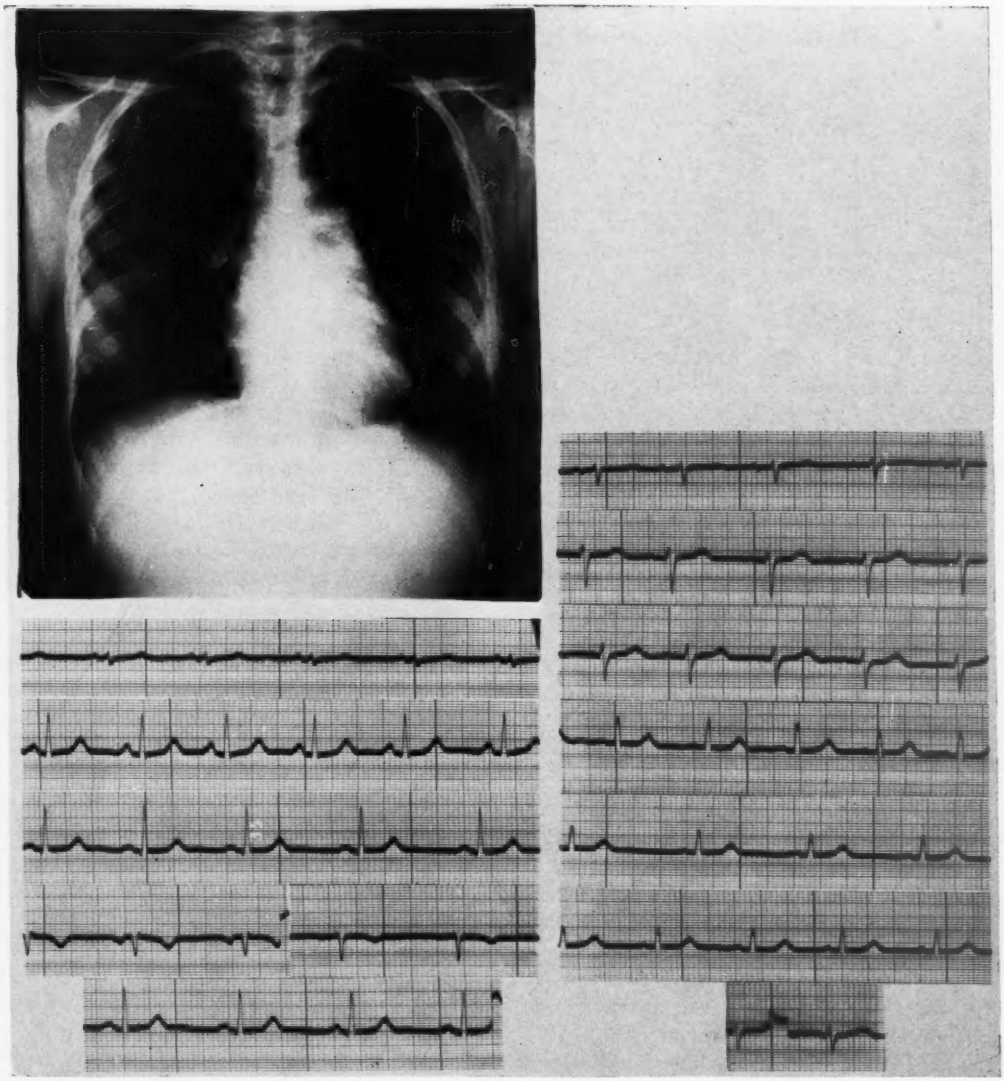

Figure 3

Chest x-ray and electrocardiogram from patient B.H. of group B. With the exception of prominence of the main pulmonary artery segment, there is no discernible difference in either x-ray or electrocardiogram as compared with the case depicted in figure 2.

resting pulmonary wedge and pulmonary artery pressures in the presence of low cardiac outputs has been noted. Indeed, Ravin and co-workers[11] suggested that such persons may compensate for their lesion by lowering blood flow rather than by elevation of pressures.

The response of the pulmonary arteriolar resistance to the increase of blood flow associated with exercise was also distinctly abnormal in group A. If the geometry of the pulmonary vascular bed is constant, a slight increase in the transmural distending pressure (left atrial, pulmonary wedge, and pulmonary artery) should result in a decrease in

Table 4

Flow and Pressure Data from Patient C.B., Group A, on Two Occasions Preoperatively, 41 Months Apart

Date	State	VO_2/M_2*	O_2 (a-v)	C.O.	C.I.	Pulmonary wedge pressure†	P.A.†	L.A.†	(LA-LV)‡	Pulmonary arteriolar resistance
4-56	Rest	132	4.1	5.6	3.2	11	21	12	10	3.1
	Exercise	351	9.6	6.5	3.9	..	46	..	..	..
9-59	Rest	100	6.1	2.9	1.6	11	15	11	11	2.5
	Exercise	503	14.8	6.1	3.5	30	57	..	..	7.6

*VO_2/M_2 is oxygen uptake per minute per meter square of B.S.A.

†Mean pressures.

‡Pressure gradient in diastole, mean.

calculated pulmonary arteriolar resistance if vascular tone remains unchanged.[13] This is, of course, a possible mechanism by which normal subjects are capable of having a large increase in flow with minimal increase in pressure; therefore, the pulmonary arteriolar resistance in normal subjects becomes smaller with exercise. The observed changes in this derived parameter in the present groups of patients would indicate that there had been a change in the physical characteristics of the pulmonary vascular bed that tended to increase pressures and calculated resistance values. An increase in active pulmonary vascular tone seems the likely responsible mechanism. The patients in group B showed no detectable abnormalities in cardiac output either at rest or during exercise. In addition, the resting arteriovenous oxygen differences were normal (fig. 1). In three of these patients the direction in which the pulmonary arteriolar resistance changed with exercise was that expected normally, i.e., a decrease.

The patients in group A represent instances in which the adjustment that the individual has made to the cardiac lesion is primarily one of an alteration in the operating level of cardiac output. In addition, pulmonary vasoconstriction may be associated with exercise. In contrast, those of group B with normal blood flow values at rest and qualitatively normal response of pulmonary arteriolar resistance to exercise can be regarded as instances in which there was a failure in adjustive mechanisms to compensate for the valvular lesion—either by alteration of blood flow or increasing vascular tone. The two members of group B who did manifest increases in pulmonary resistance evidently did compensate partially by changing pulmonary vascular tone.

As indicated above, data of two studies are available in one patient (C.B.) over a 3½-year period of observation. During this interval the symptoms tabulated in table 1 were intensified but no change in clinical signs, x-ray, or electrocardiogram was evident. It is concluded that the observed hemodynamic adjustment (in this case a lowered resting cardiac output) occurred along with a decrease in effective mitral valve area. This did not exist at the time of the first study when the obstruction was mild. This suggests that lowered flow is a finding not unrelated to, nor independent of, the degree of mitral stenosis in this group but may act in an adaptive sense to minimize the pressure manifestations of mitral valve obstruction. This conclusion is supported by the fact that all patients of group A had significant mitral stenosis.

By extrapolation it is attractive to suppose that the response of decreased flow with normal pressures may be the result of a process which is the inverse of that seen in trained athletes who demonstrate a consistently increased resting stroke volume. In the cases studied here a lowered output was the result of constantly limited demand on the requirements for cardiac output. This was accomplished by a decreased stroke volume rather than by bradycardia.

The findings in the second group studied, namely, normal flow despite increased stroke work, suggest that potent stimuli exist that maintained flow at normal values. Early pregnancy (less than 3 months) may have been the factor in cases L.C. and B.H.

The presence of such variable responses in

Table 5

Cases of Mitral Stenosis Proved at Operation or Autopsy—Resting Data

Series	Total number	Low CI* Normal PC and PA†	Low CI High PC and PA	Normal CI High PC and PA
McDonald et al.[12]	33	0	25	8
Ravin et al.[11]	16	3	13	0
Dickens et al.[10]	35	1	31	3
	84	4	69	11
%		(5)	(82)	(13)
(Present)	86	4	75	7
%		(5)	(88)	(7)

*CI, cardiac index.

†PC and PA, pulmonary wedge and pulmonary artery pressure.

12 to 18 per cent of cases with significant mitral stenosis allows for possible error in the clinical assessment of the severity of the obstructive lesion. In the first group an advanced degree of stenosis would be overlooked or underestimated. In the second group, prominent signs and symptoms would indicate a greater degree of stenosis than in fact exists.

Summary

Of a total group of 86, 11 cases of proved significant mitral stenosis with cardiovascular hemodynamic data are presented.

Four had normal pulmonary wedge and pulmonary artery pressures at rest and low cardiac index at rest and after mild exercise. It is postulated that such persons respond to mitral valve obstruction primarily by lowering cardiac output.

The cardiac index in seven was normal at rest and after mild exercise. Thus there was no evidence that alteration of blood flow had occurred in response to the lesion. The values for pulmonary arteriolar resistance in three of these were qualitatively normal when flow was increased. These are considered to be examples of absent or inadequate changes in pulmonary vascular reactivity.

The existence in a significant percentage of patients with mitral stenosis of a low cardiac output with normal resting pulmonary, arteriolar, and wedge pressures, or normal cardiac output despite elevation of these pressures infers that potent flow-regulating factors can operate independently of the obstructive lesion.

Acknowledgment

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Measurement of Mitral Regurgitation in Man from Simultaneous Atrial and Arterial Dilution Curves after Ventricular Injection

By Gilbert E. Levinson, M.D., Samuel W. Stein, M.D., Richard A. Carleton, M.D., and Walter H. Abelmann, M.D.

THE MOST DIRECT APPROACH to measurement of the volume of blood regurgitating across an insufficient mitral valve consists of the injection of indicator into the left ventricle and simultaneous sampling of blood from the left atrium and from the aorta or one of its branches. If mixing is complete in the left ventricle, the distribution of indicator to upstream and downstream collection sites is a function of the volumes of blood flowing in these directions.

This principle has been used in experimental animals and in man by a number of investigators.[1-5] Their data demonstrate a relationship between the calculated values of regurgitant flow and the clinical or surgical estimates of the severity of insufficiency. The studies referred to, however, involve only 33 patients with clinical mitral disease. Fewer than half of these had any appreciable regurgitation as judged by clinical, surgical, and physiologic criteria. Figures for actual backflow in liters per minute are provided only in one preliminary report[3] of a small series. In 20 of the cases,[4] the essential dilution curves were not obtained simultaneously. In no clinical case was a duplicate measurement described, and available data on reproducibility of this method are limited to studies of surgically produced lesions of short duration in dogs[5] and of tricuspid insufficiency in a small number of patients with lesions of limited severity.[6]

The present study was designed to evaluate this direct method for the quantification of clinical mitral insufficiency.

Materials and Methods

Twenty-four studies were performed in 16 patients with rheumatic disease of the mitral valve. Two of the patients were demonstrated at cardiac catheterization to have severe aortic stenosis, which was confirmed at surgery. Clinical, fluoroscopic, and physiologic evidence of aortic regurgitation was absent in all patients. The mitral lesion was classified as pure mitral stenosis (MS), predominant mitral stenosis with mild to moderate insufficiency (MSmr), predominant and moderate to severe insufficiency (MRms), or pure and severe mitral insufficiency (MR). In six patients in whom surgery was not performed, classification was based on clinical information and physiologic data not including the method under study.[7-9] In the 10 patients who underwent surgery, classification was based on the clinical, physiologic, and surgical findings.

Indicator-dilution curves were obtained during catheterization of the left side of the heart, performed by the percutaneous transdorsal route with the patient in the prone position and under mild barbiturate sedation. Evans-blue dye (4 to 5 mg.) was injected rapidly from a calibrated pipette[10] through a polyethylene catheter (internal diameter 0.76 mm.) into the left ventricle. Beginning shortly before the injection of dye, blood was collected simultaneously from a 7-inch, thin-walled, 16-gage needle in the left atrium and a thin-walled 16-gage Cournand needle in the brachial artery, by one of two methods. In the first method, a pump (Harvard Apparatus Co., Dover, Mass.) drew blood through 40 cm. of polyethylene tubing

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Table 1

Clinical and Physiologic Data

Patient	No.	Diagnosis	Rhythm	Injection into left atrium		Injection into left ventricle				
								Estimated regurgitant flow		
				Heart rate	Systemic flow (L./min.)	Heart rate	Systemic flow (L./min.)	L./min.	% Systemic flow	% Total ventricular output
C.W.	99	MS	AF	96	3.09	75	3.24	0	0	0
A.L.	154	MS	AF	55	3.32	64	3.32	0.10	3	3
E.L.	162	MS	AF	54	2.66	66	3.11	0.31	10	9
			AF	52	2.34					
N.P.	152	MS	AF	53	5.02	60	6.27	1.06	17	15
			AF			56	6.65	0.48	7	7
A.La.	148	MSmr	RSR	72	4.52	77	5.26	0.48	9	8
F.F.	164	MSmr	AF	96	3.40	95	2.63	0.34	13	11
A.P.	160	MSASmr	RSR	69	2.96	74	1.96	0.31	16	14
			RSR	76	2.27					
T.N.	161	MSmr	AF	80	2.65	90	3.58	0.69	19	16
			AF			116	2.93	1.11	38	28
E.K.	170	MSmr	AF	81	4.11	81	4.96	3.05	62	38
			AF	81	4.11	87	3.53	1.41	40	29
A.Lo.	151	MSmrAS	RSR	106	5.67	106	4.75	2.99	63	39
J.M.	MA62	MRms	RSR	111	4.36	119	4.97	3.00	60	38
			RSR			119	4.97	1.02	21	17
L.M.	174	MRms	RSR	75	6.23	80	5.48	4.39	80	45
			RSR	72	7.07	75	5.18	2.43	47	32
M.R.	167	MRms	AF	68	1.87	66	2.31	10.46	453	82
A.McM.	176	MR	AF	63	5.00	62	4.99	8.52	171	63
			AF			63	4.24	4.94	117	54
G.L.	159	MR	RSR	84	8.64	88	8.85	8.36	95	49
			RSR	86	10.73	88	11.80	195.95	1661	94
R.S.	172	MR	AF	74	3.76	76	2.35	5.60	238	70
			AF	90	3.77	88	4.66			>100

(internal diameter 1.13 mm.) at a constant rate of 0.7 ml. per second into a cuvette densitometer.[11] The output of the latter was recorded on a direct-writing oscillograph (Sanborn 150), and an integrated sample technic[12] was used to calibrate the curve. In the second method, blood was withdrawn intermittently through 40 cm. of polyethylene tubing (internal diameter 1.13 mm.) by means of double-valved Cornwall syringes and injected into heparinized tubes mounted at equal intervals on a rotating disk driven by a constant-speed motor. The speed of the disk and the volume of the syringe could be adjusted to permit collection of 24 samples in 30, 36, or 48 seconds. With both methods, plasma dye concentrations were determined in a spectrophotometer (Beckman Model DU) at a wavelength of 625 mμ. Hematocrit values were determined in duplicate by centrifuging heparinized arterial blood in Wintrobe tubes for 30 minutes at 2,500 rpm. The mean observed hematocrit level was multiplied by 0.96 to correct for trapped plasma.[13]

In three patients (A.L., N.P., and A.Lo.) the left atrial and brachial arterial curves were obtained by continuous densitometric recording. In two patients (C.W. and A.La.) the left atrial curves were obtained with the densitometer and the brachial arterial curves by fractional collection. In the remaining 11 patients the left atrial curves were obtained by fractional collection and the brachial arterial curves with the cuvette densitometer.

All dilution curves were plotted semilogarithmically and extrapolated to 1 per cent of peak concentration value. Areas were obtained by summation of the concentrations at 1-second intervals. Forward flow was calculated according to the method of Hamilton.[14] Mitral regurgitant flow was calculated according to the following formula:[15]

$$\dot{Q}_R = \frac{\dot{Q}_S}{(A_{SA}/A_{LA}) - 1}$$

where $\dot{Q}_R$ = regurgitant flow, $\dot{Q}_S$ = systemic cardiac output, A_{SA} = the area under the systemic

Table 2

Comparison of Paired Measurements of Systemic Flow

Item	Replicates with atrial injection	Replicates with ventricular injection	Atrial vs. ventricular injection
Mean absolute difference (L./min.)	0.66	0.82	0.68
S.E. of observation (L./min.)	0.41	0.44	0.21
Coefficient of variation (%)	8.4	7.9	4.8
Significance of mean algebraic difference	$0.4<p<0.5$	$0.8<p<0.9$	$0.9<p<1.0$

For the comparison between atrial and ventricular injection sites, the mean of replicate measurements from either site was used whenever these had been performed. Significance was determined by Student's t-test, comparing mean algebraic difference with standard error. In the atrial and ventricular replications, an identical result is obtained by analysis of variance, comparing the variance due to replication with the error variance due to patient variation in replication.

arterial dilution curve, and A_{LA} = the area under the early left atrial dilution curve.

In eight patients this study was repeated after an interval of 10 to 30 minutes. In all patients, systemic output was also measured independently from a peripheral arterial dilution curve after injection into the left atrium. In six patients, the latter measurement was repeated after an interval of 10 to 30 minutes. Differences between duplicate measurements of regurgitant flow, between duplicate measurements of forward flow with the same injection site, and between measurements of forward flow with the two different injection sites, were evaluated with standard statistical technics for small samples[16] The relationship between estimated $\dot{Q}_R$ and the diagnostic classification was measured with use of the correlation ratio eta, which is applicable whether or not the relationship is linear.[16] Further details of the technics employed in these studies have been reported previously.[17]

Results

The results of this study are presented in table 1.

Measurements of Forward Flow

The statistical analysis summarized in table 2 demonstrates that, in this series of patients, the variability in estimates of cardiac output was not greater with left ventricular than with left atrial injections, and that there was no systematic difference in estimate of cardiac output between the two injection sites. In addition, comparison of a coefficient of variation for each patient (with 1 degree of freedom) with that for the entire group (with appropriate degrees of freedom) reveals that none of the individual differences between replicates was statistically significant, and in only one patient (R.S.) did the measurement of systemic flow obtained with atrial injection differ significantly ($p < 0.05$) from that obtained with ventricular injection.

These results permit the conclusion that satisfactory estimates of systemic flow can usually be obtained with injection of indicator into the left ventricle.

Measurements of Regurgitant Flow

Validity

Figure 1 illustrates the raw data obtained in one patient in each of the four diagnostic groups in whom the dilution curves were considered satisfactory and the estimates of $\dot{Q}_R$ conformed to the clinical, physiologic, and surgical findings. It is clear that the ratio A_{LA}/A_{SA} increases with increasing severity of mitral insufficiency. In addition, as McClure et al.[18] have shown mathematically and in a cardiovascular model, the descending limb of the arterial dilution curve exhibits, in the presence of mitral insufficiency, an earlier, steeper slope, representing ventricular wash-

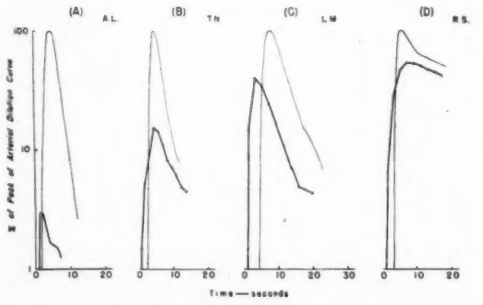

Figure 1

Semilogarithmic replots of the dilution curves obtained from one patient in each of the diagnostic categories: pure mitral stenosis (A), predominant stenosis (B), predominant mitral regurgitation (C), and pure regurgitation (D). Left atrial curves are drawn in heavy lines, brachial arterial curves in light lines. To facilitate comparison, the arterial dilution curves are drawn to peak at the same ordinal value and all other concentrations are expressed as a per cent of that peak.

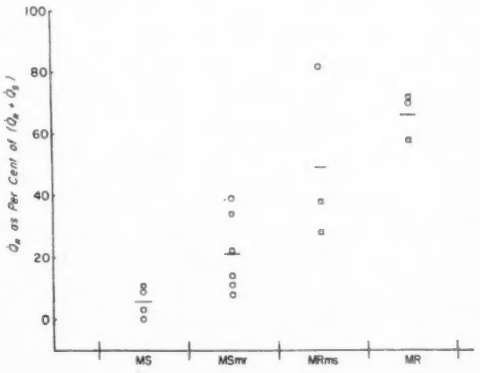

Figure 2

Scattergram showing the relation between calculated regurgitant flow ($\dot{Q}_R$) and the severity of mitral regurgitation for all patients studied. $\dot{Q}_R$ is expressed as a per cent of calculated total left ventricular output ($\dot{Q}_R + \dot{Q}_S$). The estimate of the severity of regurgitation is based upon all available clinical and surgical information. Each circle or square represents one patient; the mean of a pair of determinations is used for those pa-symbols). The horizontal line in each column indicates the mean $\dot{Q}_R$ for that group.

out, and a later, flatter slope representing atrioventricular washout. This is seen most clearly in figure 1D but is also evident in figure 1C and is suggested in figure 1B. Thus, the qualitative and quantitative features of these curves are functions of increasing severity of regurgitation.

The scattergram of figure 2 demonstrates a definite relationship between the estimated $\dot{Q}_R$ and the diagnostic classification. The overlap between groups signifies that the classification is, by necessity, an arbitrary ordinal scale for a continuous variable. For the MR and MRms groups, in particular, the data may be pooled, since purity of the lesion does not necessarily signify greater severity. The mean and range of $\dot{Q}_R$, expressed as a per cent of estimated total left ventricular output, for patients with pure mitral stenosis, predominant stenosis with mild to moderate insufficiency, and predominant or pure insufficiency, are 6 per cent (0 to 11), 21 per cent (8 to 39), and 58 per cent (28 to 82), respectively. The correlation ratio eta is 0.87, signifying that three fourths ($eta^2 = 0.75$) of the variability in estimated $\dot{Q}_R$ is a function of the changes in severity of the regurgitant lesion expressed in the diagnostic classification.

Reliability

In 10 patients, there were no clinical, physiologic, or surgical grounds for doubting the correctness of the calculated $\dot{Q}_R$. However, seven of these 10 were patients with pure mitral stenosis or predominant stenosis with minimal or mild insufficiency, in whom the opportunity for misestimate is limited. Moreover, surgery has not been performed in four of the 10 patients, including two of the three with predominant or pure insufficiency. In these cases, therefore, although the order of magnitude seems correct, the absence of an anatomic estimate of the size of the mitral valve precludes a quantitative assessment of the accuracy of $\dot{Q}_R$.

Eight studies, in six patients, gave results that were either mathematically absurd, physiologically incredible, in conflict with diagnostic evidence, or otherwise suspect.

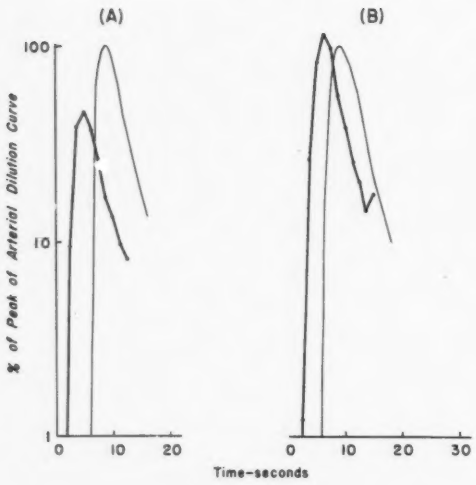

Figure 3

Semilogarithmic replot of the dilution curves obtained, after injection of indicator into the left ventricle, in the two studies performed in patient G.L. The disparity in the ratio A_{LA}/A_{SA} between the first study (A) and the second study (B), 12 minutes later, is evident. From (A), a $\dot{Q}_E$ of 8.4 L./min. was calculated while study (B) resulted in a calculated $\dot{Q}_E$ of 196 L./min.

The single study in patient A.La. seems clearly to be a case of underestimation of $\dot{Q}_R$. The surgeon described moderate (2+) regurgitation and a mitral valve area of 1.5 cm.^{2} The physiologic estimate of mitral valve size, which was based upon a total mitral diastolic valve flow equal to $\dot{Q}_S + \dot{Q}_R$, was 1.0 cm.^{2} If the surgeon's estimate is accepted as a satisfactory description of the mitral valve in this patient, then the regurgitant flow at the time of study must have been at least 2.8 L./min. or over one third of total left ventricular output, whereas the physiologic estimate was 0.48 L./min. or less than one tenth of total left ventricular output.

In patient E.K., regurgitation was overestimated. For her two studies, with use of a pressure gradient measured immediately after the flow and the sum of $\dot{Q}_R + \dot{Q}_S$ as total mitral diastolic flow, the physiologic estimates of mitral valve area were 1.1 and 1.3 cm.^{2} The surgeon found a valve of approximately half this size and described the regurgitation as mild (1+).

In patient J.M., the lower of the two estimates of regurgitant flow and the mean of the two estimates fell within the range found in predominant stenosis. The surgeon found negligible stenosis and moderately severe insufficiency.

Patient A.Lo. is of particular interest, since he had both evidence of, and a demonstrated reason for, overestimate of his mitral regurgitant flow. The surgical report in this patient was of mild (1+) regurgitation. If the surgeon's description of the diastolic mitral valve area is accepted, the expected regurgitant flow at the time of study is 2.0 L./min. or approximately 30 per cent of total left ventricular output. The dye-dilution estimate was 2.99 L./min. or 39 per cent of total left ventricular output. In previous studies,[19] however, it was demonstrated, by two independent methods, that this patient (case no. 6 in that study) had a larger-than-normal flow through bronchopulmonary anastomoses resulting in the introduction of dye into the left atrium prior to the appearance of recirculating dye. The measured pulmonary collateral flow at that time amounted to 7.2 per cent and 5.9 per cent of total ventricular output by the two methods. For this reason, it is believed that mitral insufficiency, which is definitely present in this patient but probably mild to moderate in severity, was somewhat overestimated by the dilution study.

Of the two studies in R.S., one produced a mathematically and physiologically absurd result: the area under the early left atrial curve exceeded that under the systemic arterial curve, which corresponds to a regurgitant flow exceeding the total left ventricular output.

The second study in R.S. gave rise to a credible figure for regurgitant flow. However, this study must be regarded as suspect because the net forward flow calculated with the left ventricular injection (2.35 L./min.) differed appreciably from that obtained 14 minutes before (3.75 L./min.) and 14 minutes after (3.76 L./min.) with left atrial injection. In no other study in this investigation did the net forward flow after left atrial injection differ from that after left ventricular injection by more than 25 per cent of the latter, and in only two instances did the difference exceed 20 per cent. None of the differences, except for R.S., is statistically significant. In this case, the difference (60 per cent) is too large ($p < 0.05$) to be attributed to random variation, and the patient's status was not apparently altered during the 28 minutes required for the three measurements. The reasonable conclusion is that the estimate of forward flow after left ventricular injection is incorrect in this instance. Therefore, calculation of $\dot{Q}_R$, which involves use of an area related to $\dot{Q}_S$, is invalid.

In patient G.L. (fig. 3), the arterial and atrial curves were technically satisfactory, and the two estimates of systemic cardiac output are in good agreement with a pair of estimates obtained with left atrial injection. There is, however, a striking

disparity between the magnitudes of the two left atrial curves. The first study gave rise to an estimate of backflow approximately equal to systemic flow. The second study resulted in the incredible value of $\dot{Q}_R$ of almost 200 L./min., which is over 1,600 per cent of systemic cardiac output.

The reproducibility of results was poor. After exclusion of the mathematically absurd result in one of the studies in R.S., the differences between duplicate determinations, in the remaining seven patients, were large: mean absolute difference = 17 per cent of total left ventricular output and coefficient of variation = 23 per cent. The practical significance of the latter statistic may be illustrated by patient A. Lo. in whose single study the estimated $\dot{Q}_R$ was 3 L./min. If systemic and regurgitant flows remain constant, there is approximately one chance in two that a second study will yield an estimate of $\dot{Q}_R$ either less than 2 L./min. or greater than 4.5 L./min.

Discussion

A variety of technics is available for assessing mitral insufficiency. Some are semiquantitative.[8, 9] Others, which attempt quantification, are indirect and empirical,[20, 21] require further validation,[22] or have not yet been applied in man.[18] The method under discussion is direct and theoretically sound and has held promise of providing a valid and reliable quantitative measure of $\dot{Q}_R$. From the present study, however, it is clear that, although it may have some semiquantitative clinical utility, it is not a dependable quantitative technic. This conclusion is supported by the mathematically absurd result in one patient, the physiologically incredible result in another, the gross discrepancies between physiologic and surgical findings in two others, the evidence for the influence of other short pathways, and the poor reproducibility in duplicate measurements. That such poor reproducibility is not due principally to temporal variation in $\dot{Q}_R$ is suggested by other studies,[22] in which, with a different quantitative approach, the coefficient of variation in measurement of $\dot{Q}_R$ was very much smaller. In addition, in that investigation, the coefficient of variation was approximately the same in patients with and without mitral regurgitation, indicating that variation in measurements of $\dot{Q}_R$ was a function of experimental error and that actual $\dot{Q}_R$ varied little under the conditions of study. Moreover, in the present investigation, the mathematically impossible and physiologically incredible results can only represent error of the method and indicate the extreme proportions that such error can achieve.

It seems obvious that incomplete mixing must be a principal cause of error. There is abundant evidence from cinefluorography in dogs[23, 24] and from indicator dilution studies in vitro,[25] in intact dogs,[4, 24, 25] in congenital heart disease,[26-28] and in disease of the mitral valve,[4] that anatomically complete mixing is rarely, if ever, achieved in cardiac chambers. The cinefluorographic observations of Swan and Beck[24] are of particular interest, since ventricular nonmixing was found in the presence of mitral regurgitation. Of seven cinefluorograms that showed more than a trace of mitral regurgitation, all showed ventricular nonmixing. It is also a commonplace angiocardiographic observation that, in clinical mitral insufficiency, regurgitated opaque medium does not invariably opacify the entire atrium.

Although the absence of complete and homogenous dispersion constitutes a physiologic limitation to the success of this method, it should be appreciated that such dispersion is not actually essential. What is required is that the amounts of dye sampled from the atrium by the atrial catheter and by the ventricle, and the amounts of dye sampled from the ventricle by the atrium and the aorta (including branches of the latter and the arterial catheter) be proportional to the volumes of blood sampled. This condition can be satisfied, in the absence of uniform physical dispersion, by its mathematic equivalent: random distribution and representative random sampling.

The distinction between complete mixing and its mathematic equivalent is not merely

semantic; it permits recognition that the largest source of technical error lies in the atrial catheter. As with all sampling, representativeness is a direct function of the ratio of sample size to population size. If forward flow, regurgitant flow, and total flow are large in relation to the volume of atrium and ventricle, then randomization of mixing and of sampling will fortuitously provide representative samples of atrial dye to the ventricle and of ventricular dye to the atrium and aorta. However, the flows (samples) obtained through catheters are small in relation to the volumes (populations) sampled. With arterial catheters, this is of negligible importance, (as, indeed, it must be if cardiac output can be correctly estimated from arterial dilution curves), presumably because the ventricular ejectate is homogenized in the aorta.[19, 24] However, information obtained from the atrium, especially if that chamber is enlarged, is subject to profound sampling error. It is in this respect that angiocardiography, although only semiquantitative, may have an advantage over indicator dilution.

The conclusion that the principal error is in atrial sampling is supported by the studies performed in dogs by Sinclair et al.[5] They found that reproducibility was negligibly affected by changes in the timing of injection or in the location of the ventricular catheter, but could be profoundly affected by changes in the position of the atrial catheter. The greater reproducibility of results for a given atrial sampling site in their cases as compared to the present series probably reflects the limited atrial enlargement accompanying surgically induced lesions of short duration, and illustrates the importance of the size of the atrial sample in relation to the size of the atrium.

It will also be appreciated that dispersion, whether homogenous or random, need not occur instantaneously. It is necessary only that one or the other of these conditions occurs in the ventricle prior to systole and in the atrium prior to ventricular filling. In this case, however, as has been pointed out by Lacy et al.,[29] if the atrial catheter and the left ventricle are to sample the same population, the atrial curve must permit recognition, not of the average atrial concentration, but specifically of the concentration obtaining during ventricular filling. The recording of such a step function is not possible with conventional methods such as were employed in the present study.

An additional source of error is the existence of other short pathways to the left atrium. In an earlier communication,[15] it was pointed out that injection into a ventricle and simultaneous collection from an atrium and an artery was merely a special application of a general principle theoretically applicable to the measurement of a variety of regional blood flows, central and peripheral. In the case of central flows, such as bronchopulmonary anastomoses, intracardiac shunts, and valvular regurgitation, the sine qua non is that the regional flow to be measured empties into a cardiac chamber to produce a dilution curve distinct from those of general circulation and recirculation. The coexistence of two such flows precludes the precise measurement of either. Bronchopulmonary collateral channels, which have been demonstrated to produce an early dilution curve in the left atrium following injection of indicator into the aorta, exist in normal man.[19] In the absence of bronchopulmonary disease, the flow through these collateral channels is only 1 or 2 per cent of left ventricular output,[19] and hence would make only a small contribution to the early dilution curve produced by mitral regurgitation. However, it is conceivable that this regional bed is responsible for the occasional finding of "regurgitated" dye in intact animals[4] and in patients with pure mitral stenosis, as in the studies by Woodward et al.[4] and in the present series. Moreover, the demonstrated enhancement of these collateral channels in certain bronchopulmonary diseases[19] would, if such disease coexisted with the valvular lesion, invalidate measurements of mitral regurgitation by the regional flow method.

The results may possibly be improved by certain technical refinements. The use, for

example, of a blunt-ended catheter with multiple, radially arranged orifices may enhance ventricular dispersion of dye.[5, 25] A comparable improvement in the atrial sampling system can also be conceived. The latter, however, must entail a substantially more rapid sampling rate without a proportional increase in caliber, and hence volume, of the sampling conduits, since the latter will impair the system's dynamic response.[30] The mixing requirements of this method are, moreover, very stringent. It seems unlikely that these and other technical refinements can eliminate the inaccuracy and irreproducibility demonstrated in this study, and permit a single observation to be accepted with a high degree of confidence. Thus, the need for multiple measurements will remain, and the attendant expenditure of time and labor, and the necessary prolongation of left heart catheterization studies will, in all probability, quite properly limit the application of this method. Moreover, methodologic improvements will not eliminate the occasional, possibly appreciable, error arising from the existence of bronchopulmonary collateral channels in some patients with acquired valvular heart disease.

Summary

Measurements of forward and regurgitant flow were obtained in 16 patients with rheumatic disease of the mitral valve by means of simultaneous systemic arterial and left atrial dilution curves after injection of Evans-blue dye into the left ventricle. The results indicate that satisfactory measurements of forward flow may be obtained with injections into the left ventricle and that the calculated regurgitant flow has a good correlation with the severity of mitral insufficiency, as estimated clinically and surgically. The mean and range of regurgitant flow, expressed as a per cent of estimated total left ventricular output, for patients with pure mitral stenosis, predominant stenosis with mild to moderate insufficiency, and predominant or pure insufficiency, were 6 per cent (0 to 11), 21 per cent (8 to 39), and 58 per cent (28 to 82), respectively.

Eight studies in six patients, however, gave results that were either mathematically absurd, physiologically incredible, in conflict with diagnostic evidence, or otherwise suspect. Moreover, in the seven patients in whom satisfactory duplicate studies were obtained, the reproducibility of results was poor: the mean absolute difference in successive measurements was 17 per cent of total left ventricular output and the coefficient of variation was 23 per cent of an observation.

It is suggested that the principal source of error lies in unrepresentative sampling from the left atrium in the presence of incomplete mixing of indicator with blood in the cardiac chambers. In some patients, an additional and possibly appreciable error may arise from the existence of an enhanced pulmonary collateral blood flow, which provides an alternative short pathway from the left ventricle to the left atrium.

It is concluded that, with conventional sampling technics, this theoretically sound approach is too capricious to be a dependable quantitative method.

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Effect of Antibiotics on the Serum Cholesterol Concentration of Patients with Atherosclerosis

By ALFRED STEINER, M.D., ELLIOTT HOWARD, M.D., AND SUAT AKGUN, M.D.

A PRELIMINARY STUDY[1] from this laboratory indicated that the oral administration of neomycin was associated with a significant decrease in serum cholesterol concentration in all of 10 patients. This investigation was prompted by the chance observation that a fall in the level of serum cholesterol occurred in a patient coincident with the oral administration of neomycin, 2 Gm. daily, in the treatment of a gastrointestinal infection due to Salmonella Tennessee. Additional studies are now presented together with experiments designed to clarify the mechanism of action of neomycin in lowering the serum cholesterol level. Evaluation of the effects of other antibiotics on the serum cholesterol levels is also reported.

Method

Fifteen male and nine female patients, aged 21 to 72 years, represent the subject material. Twenty-one were hospitalized and three were observed as outpatients. The clinical diagnosis of each subject is listed in table 1. Total serum cholesterol levels were determined by the method of Abell et al.[2] twice weekly in the hospitalized subjects and at weekly or biweekly intervals in the outpatients. The ester fraction was determined by the method of Schoenheimer and Sperry.[3] Total serum lipid values were obtained by a gravimetric procedure.[4] lipid phosphorus by the method of Fiske and Subbarow,[5] and alpha- and beta-lipoproteins by paper electrophoresis.[6]

Seventeen of the 21 hospitalized patients were on the regular hospital diet of 2,200 calories, with 45 per cent of the calories derived from fat; one (Nas) received a diabetic diet of carbohydrate 180 Gm., protein 80 Gm., fat 80 Gm. without insulin, one (Ber) with familial hypercholesteremia was on a low-fat diet in which 25 per cent of the calories were derived from fat; two (Lew, Les) were maintained on a similar low-fat diet after a preliminary period of 6 weeks on the regular hospital diet. The three outpatients ate an unrestricted and unknown diet during the study.

Average control serum lipid values were established during periods of 4 to 14 weeks (mean 6.7 weeks) prior to administration of the antibiotics. The number of control determinations averaged 12.7 per patient. Oral neomycin was the initial drug studied and was given at the following daily dose level: 0.5 Gm. during five periods, 1 Gm. during five periods, 1.5 Gm. during two periods, 2 Gm. during 15 periods, and 4 Gm. during two periods. The duration of the periods of drug administration varied from 4 to 36 weeks, the mean was 8.5 weeks. In four patients, successive increasing amounts of neomycin were given after 4 to 6 weeks at each dose level without intervening control periods. At the termination of the oral neomycin, a second control period of 5 to 12 weeks was carried out. Many of the subjects were then tested with other oral antibiotics including kanamycin, bacitracin, achromycin, aureomycin, chloromycetin, mycostatin, and streptomycin as well as the following antibiotics given by intramuscular injection: neomycin, streptomycin, and penicillin.* In each instance, a control period of observation preceded the administration of each drug, or each special study when it was desirable to evaluate the effects of a combination of antibiotics.

An alteration of 10 per cent or more from the mean serum cholesterol value of the control period has been found to be necessary to have statistical significance. In a previous report[7] from this laboratory, it was shown that the serum cholesterol level in patients with coronary atherosclerosis is inconstant and varies widely. The standard deviation of the mean serum cholesterol values in

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Table 1

Effect of Oral Neomycin on Serum Cholesterol

Patient, sex, age, diagnosis	Control			Neomycin				
	Weeks	No. of determinations	Average total cholesterol mg./100 ml.	Gm.	Weeks	No. of determinations	Average total cholesterol	Average fall %
1. PUP, F, 59, cerebral thrombosis	5	11	233 ± 37*	0.5	4	9	189 ± 33	19
2. PUP, F, 59, cerebral thrombosis	5	11	233 ± 37	1.0	4	8	198 ± 23	15
3. PUP, F, 59, cerebral thrombosis	5	11	233 ± 37	1.5	4	8	174 ± 21	25
4. WAL, M, 58, hyperten. heart dis.	6	12	237 ± 23	0.5	6	11	202 ± 32	15
5. WAL, M, 58, hyperten. heart dis.	6	12	237 ± 23	1.0	6	10	186 ± 25	22
6. WAL, M, 58, hyperten. heart dis.	8	15	223 ± 25	2.0	8	16	163 ± 31	27
7. LEW, M, 69, cerebral thrombosis†	9	18	194 ± 23	1.0	4	8	172 ± 11	11
8. LEW, M, 69, cerebral thrombosis	9	18	194 ± 23	1.5	6	12	157 ± 13	19
9. NAS, M, 50, rheumatic heart dis.	3	6	241 ± 14	0.5	4	9	204 ± 30	15
10. NAS, M, 50, rheumatic heart dis.	7	16	230 ± 18	2.0	7	14	187 ± 61	19
11. BER, F, 52, familial hypercholesteremia, coronary art. dis.†	5	10	405 ± 33	2.0	5	20	331 ± 22	18
12. LES, M, 72, coronary art. dis.†	8	16	233 ± 33	2.0	5	10	189 ± 25	19
13. LES, M, 72, coronary art. dis.†	14	27	224 ± 40	4.0	5	10	180 ± 18	19
14. OST, M, peripheral neuritis	9	15	266 ± 23	2.0	4	8	209 ± 18	21
15. OST, M, peripheral neuritis	8	14	241 ± 36	2.0	6	13	182 ± 52	24
16. BER, F, 21, familial hypercholesteremia	5	5	366 ± 8	2.0	6	7	279 ± 63	24
17. HAM, F, 36, familial hypercholesteremia	5	10	442 ± 35	2.0	3	2	367	17
18. WAL, M, 64, coronary art. dis.	6	11	188 ± 45	2.0	3	2	134	29
19. SIL, M, 68, coronary art. dis.	6	11	180 ± 14	1.0	15	29	138 ± 41	23
20. GOF, M, 62, coronary art. dis.	6	12	218 ± 35	2.0	15	29	178 ± 36	18
21. HRO, F, 68, cerebral thrombosis	6	10	270 ± 52	2.0	7	13	243 ± 89	10
22. HRO, F, 68, cerebral thrombosis	6	10	270 ± 52	4.0	4	7	208 ± 33	23
23. SCA, M, 60, emphysema	4	9	187 ± 23	2.0	7	12	160 ± 50	14
24. KAT, F, 52, coronary art. dis.	5	5	313 ± 17	1.0	6	5	282 ± 17	10
25. CON, F, 65, cerebral thrombosis	6	12	236 ± 36	2.0	8	14	189 ± 22	20
26. GOL, M, 64, coronary art. dis.	8	4	299 ± 10	0.5	12	6	248 ± 8	17
27. TRL, M, 54, coronary art. dis.	8	4	318 ± 12	0.5	12	6	242 ± 18	23
28. BAL, F, 68, cerebral thrombosis	8	4	323 ± 26	2.0	36	68	249 ± 56	23
29. SCH, F, 70, cerebral thrombosis	8	4	246 ± 17	2.0	36	68	170 ± 26	30

*Maximum deviation from the mean.

†Low-fat diet during control period.

patients with coronary atherosclerosis was almost three times the standard deviation of control subjects. The difference between mean serum cholesterol values of any control and treatment period should thus approximate 10 per cent in order to have statistical significance. In the present study, there was no exclusion of serum lipid values during transition periods when the antibiotics tested had not become fully effective.

Results

Neomycin

The results of the oral administration of neomycin to 20 patients during 29 periods are summarized in table 1. The amount of oral neomycin given daily varied from 0.5 to 4 Gm. The duration of therapy varied from 4 to 36 weeks, the mean was 8.5 weeks. After the initiation of oral neomycin, the serum cholesterol level decreased significantly and usually reached the lowest level after 2 weeks (figs. 1 and 2). This decrease in serum cholesterol was maintained for the duration of the neomycin period. In some instances, to keep the serum cholesterol at the low point, the amount of neomycin was increased from 0.5 or 1 Gm. daily to 1.5 or 2 Gm. daily (fig. 1).

Increasing the amount of oral neomycin from 0.5 to 2 Gm. tended to increase the average fall in the level of serum cholesterol. At a dose of 0.5 or 1 Gm. daily (10 periods) the

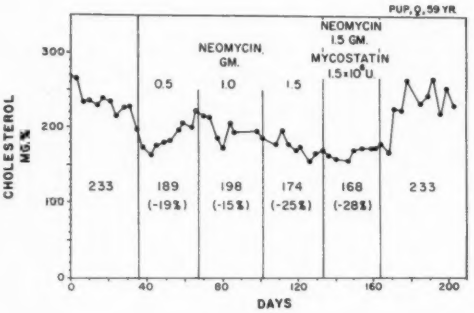

Figure 1

Effect of oral neomycin on serum cholesterol.

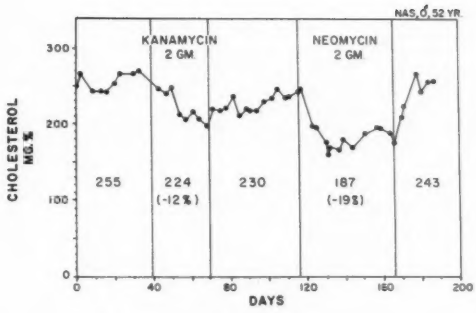

Figure 2

Effect of oral antibiotics on serum cholesterol.

average decrease of the mean serum cholesterol concentration of each period was 17 per cent, at 1.5 or 2 Gm. daily (15 periods) the average fall in the mean serum cholesterol concentration was 20 per cent. When the amount of the drug was increased to 4 Gm. (2 periods) the average fall in the mean serum cholesterol concentration was 22 per cent. The neomycin was not increased further because this 2 per cent additional fall did not appear large enough to warrant further study. It was also considered that possible toxic effects of the drug might appear.

In the 29 periods of neomycin administration to 20 patients, the fall in average serum cholesterol of each period varied from 10 to 29 per cent, the average being 21 per cent. When oral neomycin was discontinued, the serum cholesterol level returned to control values, usually in 2 weeks (figs. 1 and 2).

The prior lowering of the serum cholesterol by a low-fat diet did not prevent a further decrease in serum cholesterol by oral neomycin. In three patients (Lew, Les, Ber), a low-fat diet (25 per cent of calories from fat) for 4 to 6 weeks resulted in an average fall in the serum cholesterol level of 10, 12, and 18 per cent. Neomycin (1.5 Gm. daily) was then added to this program and caused a further fall in the average serum cholesterol concentration of 20, 18, and 17 per cent, respectively. In contrast unpublished studies have demonstrated that the feeding of unsaturated fats to patients on low-fat diets will not further decrease the serum cholesterol values.[8]

Oral neomycin is poorly absorbed from the gastrointestinal tract, and it has been determined that 97 per cent of the neomycin so administered can be recovered in the stools.[9] The action of neomycin may be due to the effect locally in the intestinal wall or on the intestinal contents. Two patients were given 60 mg. of neomycin intramuscularly daily for 2 weeks without any appreciable change in the serum cholesterol level. This amount of neomycin was calculated to exceed that proportion of the drug that is absorbed from the gastrointestinal tract.

In addition to a fall in serum cholesterol concentration, oral neomycin resulted in a decrease in total serum lipids in each of the patients, the average fall being 23 per cent.

The esterified fraction of serum cholesterol decreased in the serum in proportion to the fall in total serum cholesterol. The serum phospholipids also decreased in a similar proportion to the fall in serum cholesterol with the cholesterol/phospholipid ratio remaining unchanged. The alpha- and beta-lipoprotein ratios were not significantly altered by neomycin.

Kanamycin

Kanamycin is chemically closely related to neomycin and is also poorly absorbed from the gastrointestinal tract. Ten periods of oral kanamycin administration have been studied in seven patients. After a prior control pe-

Table 2

Effect of Oral Kanamycin on Serum Cholesterol

	Control			Kanamycin				
Patient	Weeks	No. of determinations	Average total cholesterol mg./100 ml.	Weeks	No. of determinations	Average total cholesterol	Difference %	Dose Gm.
1. Nas	5	8	256 ± 14	4	8	224 ± 27	−12	2
2. Les	5	10	218 ± 16	3	6	216 ± 10	0	2
3. Les	5	10	218 ± 16	3	5	201 ± 5	− 8	4
4. Ost	5	11	239 ± 25	4	7	250 ± 30	+ 5	2
5. Ost	5	11	239 ± 25	6	11	237 ± 36	− 5	4
6. Lew	12	26	184 ± 18	4	8	171 ± 10	− 7	2
7. Sea	10	20	179 ± 31	4	9	187 ± 12	+ 4	2
8. Wal	6	12	228 ± 19	5	10	192 ± 33	−15	2
9. Wal	6	12	228 ± 19	6	13	169 ± 8	−25	4
10. Con	8	11	211 ± 23	4	7	214 ± 38	0	2

riod, the drug was given daily in amounts of 2 Gm. for 3 to 5 weeks in seven instances. In two of the drug periods, a significant fall in the serum cholesterol level occurred, averaging 13.5 per cent (table 2 and fig. 2). At the 4-Gm. dose level in three trial periods, there was one instance of a significant fall (greater than 10 per cent) in the level of serum cholesterol.

Although kanamycin produced a fall in serum cholesterol in 3 of 10 instances, its effect is smaller and less consistent than that of neomycin.

Streptomycin and Bacitracin

The combination of intramuscular streptomycin plus oral bacitracin was thought likely to result in a similar effect as oral neomycin on the bacterial flora of the gastrointestinal tract. One gram of streptomycin (intramuscular) plus 2,500 units of oral bacitracin were given to three patients for 2 weeks after an initial control period. No significant alteration of the serum cholesterol level occurred. At the end of 2 weeks, 2 Gm. of oral neomycin was added to the streptomycin and bacitracin and in each instance, a significant fall in serum cholesterol level occurred. After 2 weeks of the three medications, the bacitracin and streptomycin were discontinued and the patients continued on the oral neomycin for one additional week. The fall in serum cholesterol level was maintained in each of the three patients (table 3 and fig. 3).

Aureomycin

In the previous experiment, when the oral neomycin was stopped, the three patients were transferred to oral aureomycin, 1 Gm. daily for 2 weeks. In one patient, the serum cholesterol level fell further, while in the remaining two patients, the serum cholesterol level increased but did not return to the control level. Additional studies on the effect of aureomycin on the serum cholesterol level are contained in table 4 and figure 4. It can be seen that oral aureomycin (1 Gm. daily for 2 weeks) was prescribed for five periods to four patients. In three of the five periods, a significant fall (greater than 10 per cent) in the serum cholesterol occurred averaging 17 per cent. In two periods, the decrease in serum cholesterol was not significant. Aureomycin had a similar but less marked effect than neomycin on the serum cholesterol level.

Achromycin

Achromycin was administered orally for six periods, 1 Gm. daily for 2 weeks, to four patients. In two instances, the average fall in serum cholesterol level was at borderline significance, while in four periods, the average decrease was less than 10 per cent.

Chloromycetin

Chloromycetin was given orally to three patients at the dose level of 1 Gm. daily for 2 weeks without any significant alteration of the serum cholesterol level.

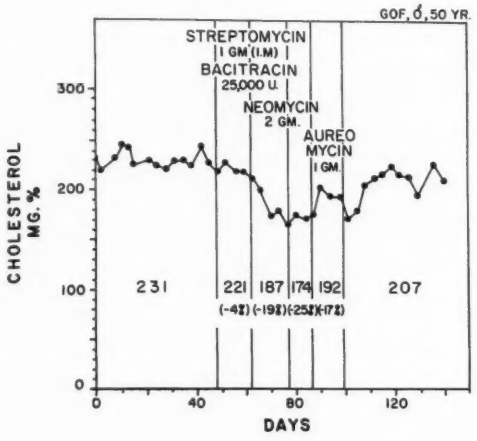

Figure 3

Effect of oral antibiotics on serum cholesterol.

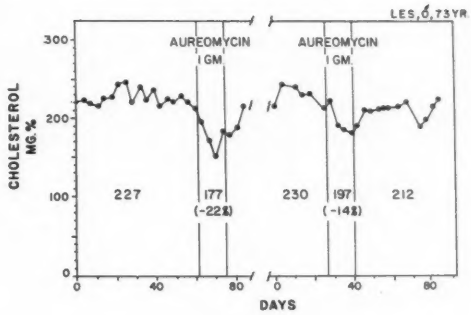

Figure 4

Effect of oral antibiotics on serum cholesterol.

Mycostatin

Oral mycostatin has been administered alone and in conjunction with oral neomycin. Two million units of mycostatin were given for seven periods of 2 weeks to five patients. In three instances, decreases of borderline significance in serum cholesterol level occurred. When mycostatin was given in conjunction with oral neomycin, the same decrease in serum cholesterol concentration occurred as when neomycin alone was given (fig. 2). Mycostatin did not appear to potentiate or decrease the effect of neomycin.

Streptomycin

Oral streptomycin (2 Gm. daily) was administered to two patients for 2 weeks without producing an alteration of the level of the serum cholesterol.

Penicillin

Intramuscular crystalline penicillin, 1.2 million units daily, was given to three patients for 2 weeks and resulted in no effect on the level of the serum cholesterol.

Discussion

The results presented revealed that oral neomycin consistently produces a significant, sustained fall in the level of serum cholesterol. Of the other antibiotics tested, in a limited number of patients, aureomycin and kanamycin resulted in less consistent and less marked decreases in the level of serum cholesterol. Oral achromycin, chloromycetin, bacitracin, streptomycin, mycostatin as well as intramuscular streptomycin, penicillin, and neomycin were ineffective.

A number of studies were designed to throw some light on the possible mechanism of action of neomycin. Preliminary studies of bacteriologic content of stools reveal that oral neomycin produces a profound effect upon the intestinal flora. Stool cultures during control periods were compared with those obtained during the neomycin period. *Escherichia coli* were most effected; with a marked reduction to absence of these organisms from the stool. There is also a suppression of the other enteric organisms except for the enterococci and *Clostridium welchii* which tend to become more abundant. Further studies of the effect of neomycin upon the intestinal flora are necessary before the mechanism of action of neomycin can be attributed to its bacteriostatic action.

An alteration in the absorption of fat from the gastrointestinal tract has been considered as one of the possible mechanisms of action of neomycin. For this reason, in cooperation with Dr. A. R. Wertheim, oral fat tolerance tests were carried out in eight patients prior to and during the oral administration of neomycin. The test meal consisted of 300 ml. of medium cream (28 per cent fat). In addition

Table 3

Effect of Antibiotics on Serum Cholesterol

	Control		Streptomycin 1 Gm./day Bacitracin 25,000 Units/day (4 weeks) (2 Weeks)		Neomycin 2 Gm./day (3 weeks) (2 Weeks)		(1 Week)		Aureomycin 1 Gm./day (2 weeks)	
	Average total cholesterol mg./100 ml.	No. determinations	Average total cholesterol mg./100 ml.	No. determinations	Average total cholesterol mg./100 ml.	No. determinations	Average total cholesterol mg./100 ml.	No. determinations	Average total cholesterol mg./100 ml.	No. determinations
Gof	230 ± 15	8	221 ± 8	4	187 ± 28	5	174 ± 3	2	192 ± 14	4
Nas	249 ± 22	9	237 ± 2	4	185 ± 50	5	177 ± 20	2	214 ± 25	4
Sca	202 ± 18	9	194 ± 10	3	168 ± 14	4	162 ± 4	2	157 ± 9	4

Table 4

Effect of Oral Aureomycin on Serum Cholesterol

	Control Before medication			Aureomycin (1 Gm. daily)				Control After medication			
	Weeks	No. of determinations	Average total cholesterol mg./100 ml.	Weeks	No. of determinations	Average total cholesterol mg./100 ml.	Difference %	Weeks	No. of determinations	Average total cholesterol mg./100 ml.	Difference % (from first control)
Arr	8	7	188 ± 22	2	4	173 ± 17	− 7.9	6	10	195 ± 36	+ 3.7
Ost	8	14	238 ± 28	2	4	202 ± 15	−15	8	16	227 ± 48	− 4.6
Les	8	18	227 ± 20	2	4	177 ± 23	−22	5	8	219 ± 39	− 3.5
Les	4	6	230 ± 15	2	4	197 ± 28	−14.3	8	16	206 ± 28	−10.4
Gof	8	15	211 ± 15	2	4	203 ± 23	− 3.8	3	6	205 ± 10	− 2.8

to determination of the serum lipids, the turbidity of the serum was measured. During the neomycin period the response of the serum turbidity was altered so that the wide range of turbidity exhibited by the patients with atherosclerosis was replaced by the response obtained in healthy "control" subjects. The various serum lipid moieties revealed less response to the fat meal when the patients were on neomycin than in the absence of the drug. This difference, however, was not remarkable.

Jacobson et al.[10] have reported the production of a malabsorption syndrome induced by the ingestion of 12 Gm. of neomycin daily. This large amount of medication produced a steatorrhea as well as diarrhea in most patients. Goldsmith et al.[11] has reported increased fecal excretion of bile salts coincident with oral neomycin administration.

In the present study, significant diarrhea did not occur. Several loose stools daily for short periods were recorded in three patients. It was not necessary to discontinue the medication in any individual. Steatorrhea was not encountered. The weights of our subjects were not altered significantly during this study.

No evidence of renal or hepatic damage due to neomycin was demonstrated by the usual laboratory determinations.

Summary

Oral neomycin, at the dose level of 0.5 to 2 Gm. daily, produced a significant fall in the level of serum cholesterol in all of 29 periods in 20 patients studied. The effect reached a maximum in approximately 2 weeks and persisted for the duration of the experiments up to 9 months. After the medication was discontinued, the serum cholesterol levels returned to control values within 2 weeks. No significant toxic reaction to oral neomycin was discernible. Neomycin by injection in excess of the amount calculated to be absorbed from the gastrointestinal tract failed to lower the serum cholesterol level. The mechanism of action of neomycin was not determined, but it is

thought to be a local effect in the gastrointestinal tract or its contents.

Oral aureomycin and oral kanamycin had a similar but less marked and less consistent effect on the level of serum cholesterol in a number of patients. In a limited number of patients, oral achromycin, bacitracin, chloromycetin, streptomycin, and mycostatin did not have a significant effect on the serum cholesterol level; likewise, intramuscular penicillin and streptomycin failed to alter the serum cholesterol level.

The prior lowering of the serum cholesterol concentration by a low-fat diet did not prevent a further decrease in the serum cholesterol by oral neomycin.

Acknowledgment

The authors are indebted to Drs. J. Bakke and M. Finkel for their helpful assistance in the clinical care of the patients in this study.

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Experience

In beginning teaching twenty and more years ago, I determined that the basis of what I taught should be that which I myself had seen and proved to be true. A second ideal that I have striven hard to attain is simplicity in teaching; this was not so easy during the years in which my work lay largely amongst pulse and galvanometric curves. But I have become more and more convinced of the need for simplicity; and it was apparent that little of the graphic work could profitably be taught to men entering practice, whose foremost interest must always be in observations they themselves can make upon their patients.—Sir Thomas Lewis. *Diseases of the Heart.* New York, The MacMillan Company, 1933, p. v.

The Exercise Test and Prognosis of Coronary Heart Disease

By GEORGE E. DIMOND, M.D.

THE SIGNIFICANCE and prognostic value of the exercise test in coronary heart disease remain controversial. Robb and associates[1] found significantly higher rates of death and occlusion in those with a positive test and stated that a negative response to the double two-step exercise test excludes, for practical purposes, the presence of latent coronary insufficiency and clinically significant narrowing of the coronary arteries. Lepeschkin[2] reported that a completely normal electrocardiographic response to the double Master exercise test indicates with great probability that no major coronary stenosis is present, or, if present, it is well compensated by collateral circulation. Wood and associates[3] permitted 100 patients with classical angina pectoris to exercise until symptoms developed and obtained an ischemic response in 88 per cent. Scherf[4] stated that it is apparently impossible to exclude false-negative tests and that any conclusion as to prognosis, based on the outcome of an exercise test, is unjustified.

The type of response to exercise in which the S-T segment is depressed 0.5 mm. or more below the P-R or P-Q junction in a horizontal or sagging course has been described as significant of myocardial ischemia by Wood and associates[3] and by Myers and Talmers.[5] Robb and associates[1] found this to be the best and only unequivocable criterion for a positive test. Brody[6] examined 756 business executives free of clinical coronary heart disease and found 23 with this ischemic type of response. Definite coronary artery disease later developed in 70 per cent of these 23 men. Myers and Talmers,[5] Robb and associates,[1] and Brody[6] all found that S-T junctional depression, if deep and not due to tachycardia, could indicate myocardial ischemia in some cases.

From the Medical Department, New York Central Railroad, Detroit, Michigan.

This report is a 5-year follow-up study of 153 railway operating employees with known or suspected coronary artery disease who were examined with an exercise test to estimate their ability to continue work in a vigorous and responsible occupation.

Material and Methods

Railway operating employees are subject to periodic examinations to determine physical fitness. Those with cardiovascular diseases are followed closely and, under the direction of the late Gordon B. Myers, electrocardiograms have been used routinely in the medical director's office since 1938. One purpose of these examinations is the detection of latent or concealed coronary artery disease, and the electrocardiographic exercise test is used in selected cases.

The men in this report were actively employed when tested, and the majority were being followed for cardiovascular disease. Thirty-six had returned to work after a myocardial infarction, 83 had hypertension or valvular heart disease, 25 had chest pain suggesting angina pectoris, and nine were obese or had diabetes. None taking digitalis was included.

Indications for an exercise test were minor depressions of the S-T segment or the S-T segment junction, and lowered or flattened T waves, particularly when these findings were a change from previous electrocardiograms. It was recognized in many men that these changes were probably due to hypertension, and the exercise test was performed to detect coexistent coronary artery insufficiency.

Another indication was chest pain suggesting angina when the resting electrocardiogram was normal or not diagnostic of acute subendocardial injury. In men with recent onset of pain or progressively severe pain, the exercise test was postponed till it was clear that acute infarction was not impending. Some hypertensive passenger engineers, because of their increased responsibility, were tested despite normal electrocardiograms and freedom from symptoms. The major characteristic of the resting electrocardiograms is shown in table 1.

For practical reasons, all men did the same amount of exercise consisting of 40 ascents of the

Table 1

Major Characteristics of Resting Electrocardiograms

Resting electrocardiogram	Number
Old myocardial infarction	37
Left ventricular hypertrophy or strain	61
Normal	42
Normal, except for nonspecific S-T segment or T-wave changes	13

standard 9-inch step described by Master.[7] They were asked to do the exercise as rapidly as they could with comfort. Almost all completed the test in 60 to 90 seconds. Since the average age of these men was 59 years, and most were of average weight, this test is roughly equivalent to or in excess of the double Master exercise test.[7] One electrocardiogram was taken immediately after exercise, in most instances with leads V_8 through V_1 followed by the unipolar and standard leads in reverse order as recommended by Myers and Talmers.[5] Those with a typical ischemic response after exercise were considered to have positive tests. The remainder, including those with S-T junctional changes, were considered negative.

The exercise tests were done prior to January 1, 1956, and all men were followed to January 1, 1961. The incidence of myocardial infarctions and causes of death during the follow-up period were determined by re-examinations, reports from attending physicians, death certificates, and records of the United States Railroad Retirement Board. In those dying suddenly, the diagnosis of myocardial infarction on the death certificate was accepted.

Results and Discussion

Thirty-seven tests were positive and 116 were negative. The incidence of myocardial infarction during the 5-year follow-up period after the test was approximately three times greater in those with a positive test and the death rate was almost double. These differences are of statistical significance. In those with an ischemic response all but two of the deaths were due to myocardial infarction. Half of the deaths in the group with a negative test were due to myocardial infarction and the remainder was largely due to complications of hypertension. The prognosis of some in the negative group was adversely effected by hypertension, and the test is probably a greater discriminator regarding survival than is shown in table 2.

Table 2

Response to Exercise and Incidence of Myocardial Infarction and Death Five Years after Test

Response to exercise	Number	Myocardial infarcts	Dead
Positive	37	16 (43%)	13 (35%)
Negative	116	16 (14%)	22 (19%)

Twenty-one men with a positive response to exercise escaped a myocardial infarction during the 5-year period after the test. Eighteen are living. One died of a myocardial infarct 10 years after a positive test and two died of causes not related to coronary heart disease. The average duration of life to date after the recording of a positive test is 7 years. Six men are still actively employed, nine retired in the usual manner between ages 65 and 70, and five retired for disability usually due to coronary artery insufficiency. The better prognosis observed in more than half of those with positive tests is presumably due to the development of better collateral circulation, which allowed them years of productive life after an ischemic response was recorded.

Eleven men were thought to have classical angina pectoris despite a normal resting electrocardiogram and a negative response to exercise. Seven had a myocardial infarct within 6 years and three others retired for incapacitating angina. In view of their symptoms and subsequent history, these men were considered to have false-negative tests.

The medical director does not base disability on the results of the exercise test alone. Those with positive tests were permitted to continue work if incapacitating symptoms were not present. Some were restricted to positions in which sudden death or disability would not be hazardous to others. Three men were temporarily removed from service because of a marked ischemic response to exercise, despite minimal symptoms. None complained of pain following the test, and no myocardial infarctions were precipitated. If complications are to be avoided, the test

should not be used when preinfarction angina is suspected, and the amount of exercise used should not greatly exceed that encountered by the man in his daily activities.

Left ventricular hypertrophy or strain in the resting electrocardiogram may lead to a false impression of an ischemic response after exercise. The S-T segment may sag more without significant depression of the S-T segment junction, or the S-T segment may be depressed due to tachycardia without change in its contour. Only those tests in which the whole S-T segment is depressed and the contour of the segment is significantly changed from the resting stage should be considered ischemic.

Summary and Conclusion

In a 5-year follow-up study of 153 railway operating employees examined with an exercise test, the incidence of myocardial infarction was approximately three times greater in those with a typical ischemic response and the death rate was almost double.

The ischemic response to an exercise test indicates transient coronary artery insufficiency and has prognostic implications of statistical significance in a large group. Application of these prognostic implications to the individual is limited by the frequency of false-negative tests and the presumed ability of collateral circulation to compensate for coronary artery insufficiency.

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Religio Medici

Lastly, if length of Days be thy Portion, make it not thy Expectation. Reckon not upon long Life: think every day the last, and live always beyond thy account. He that so often surviveth his Expectation lives many Lives, and will scarce complain of the shortness of his days.—Sir Thomas Browne. *Religio Medici,* 1642, edited by W. A. Greenhill, M.D., Oxon., London, MacMillan and Co., Limited, 1950, p. 231.

Surgical Relief of Diffuse Subvalvular Aortic Stenosis

By JOHN W. KIRKLIN, M.D., AND F. HENRY ELLIS, JR., M.D.

CONGENITAL valvular aortic stenosis and congenital localized subvalvular aortic stenosis are commonly encountered, easily recognized at operation, and relieved by standard surgical technics. Idiopathic diffuse subvalvular aortic stenosis is uncommon and can be overlooked at operation. Its relief by indirect methods has been proposed by some because of the problems inherent in its exposure in direct surgical relief.

In two cases an excellent result has been obtained by exposure and direct surgical excision of the lesion through a small left ventriculotomy. The technic appears generally applicable to this lesion.

Identification at Operation

Patients with congenital aortic stenosis should be known to have a systolic pressure gradient between the left ventricle and aorta prior to operation. When such a patient is found at operation to have a normal aortic valve and no localized stenosis immediately beneath the aortic cusps, the diagnosis of diffuse subvalvular aortic stenosis is to be strongly suspected. This type of obstruction usually cannot be visualized through the leaflets (figs. 1 and 2). The diagnosis can be made positively, however, by passing the left index finger into the aortotomy and through the aortic valve into the cavity of the left ventricle, with the thumb remaining outside the heart. The characteristic diffuse thickening situated 1 to 2 cm. upstream from the aortic valve can then be palpated between the thumb and index finger. It is most readily appreciated along the ventricular septum.

From the Mayo Clinic and the Mayo Foundation, Rochester, Minnesota.

Technic of Resection

Extracorporeal circulation is established as usual by utilizing a single large venous cannula in the right atrium to divert caval blood to the extracorporeal apparatus. A catheter is inserted through the left atrial appendage into the left atrium and attached to the intracardiac sucker system. The aorta is cross-clamped and the ascending aorta is opened between clamp and aortic valve. After identification of the lesion, an incision about 2.5 cm. long is made in the free wall of the left ventricle. The optimal point for this incision is selected with the left index finger in the left ventricle to palpate the most accessible and thinnest portion of the anterior ventricular wall. Due regard is taken of the distribution of the coronary arteries so that the ventriculotomy incision does not compromise any large branches.

Small catspaw retractors are placed in the ventriculotomy incision. The chordae, papillary muscles, and anterior leaflet of the mitral valve can be visualized, although with some difficulty, through this small incision in a thick ventricle (fig. 3). The aortic leaflets cannot be visualized, but the left index finger can be kept in the aortotomy incision against the aortic leaflets to identify their location during the early stages of the resection.

The hypertrophied musculature is excised. The use of a Brock punch was helpful in one of our cases, but in most cases excision is done best by sharp dissection with a knife, or scissors, or both. Because of the dangers involved in resecting near the mitral valve structures, most of the resected material is taken from the region of the ventricular septum and the anterior portion of the free wall of the left ven-

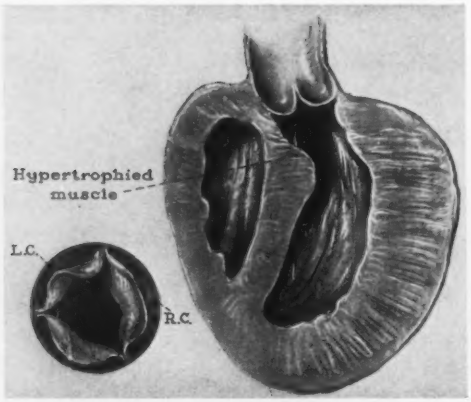

Figure 1

Anatomy of diffuse subvalvular aortic stenosis. The obstructing hypertrophied portion of muscle is about 1 cm. upstream from the base of the valve and is considerably more prominent during ventricular systole. For these reasons, at operation, with the heart quiet and the base of the aorta opened, no obstruction is visible in or beneath the aortic valve.

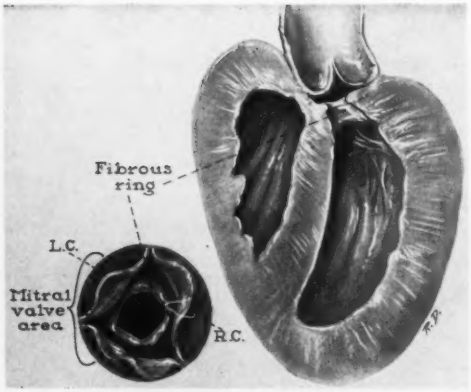

Figure 2

Localized subvalvular aortic stenosis. Note that the obstruction, which is partly fibrous, is immediately beneath the base of the aortic valve leaflets. It is clearly visible at operation through the aortotomy incision.

tricle. The outflow tract of the ventricle can be greatly enlarged by resection of this muscle mass, just as in cases of subvalvular pulmonary stenosis secondary to valvular pulmonary stenosis.

Direct perfusion of the coronary artery was not employed in either of the cases we are reporting, since resection could be accomplished within 20 to 25 minutes. The root of the aorta is closed and the aortic clamp is released, thus allowing coronary perfusion to begin. After the heart has begun to beat and with the ventriculotomy still open, one can palpate the outflow tract of the left ventricle in order to determine whether sufficient tissue has been removed to relieve the obstruction. If it has, the left ventriculotomy is closed with interrupted silk sutures, and air is evacuated from the ventricle. Perfusion is gradually discontinued in the usual fashion.

Report of Cases

Case 1

A 17-year-old white boy had noted fatigue, dyspnea, and substernal tightness from moderately severe exertion for about 2 years prior to his admission to the Mayo Clinic. His family history was noncontributory. Physical examination revealed a coarse systolic murmur in the aortic area. A roentgenogram of the thorax revealed evidence of a possible enlargement of the left atrium. The electrocardiogram gave evidence of left ventricular hypertrophy. The blood pressure was 90 mm. of mercury systolic and 60 mm. diastolic. By percutaneous punctures, systolic pressure was found to be 175 mm. of mercury in the cavity of the left ventricle while that in the aorta was 100 mm.

Operation was performed on April 9, 1959. At operation pressure was found to be 159 mm. of mercury systolic in the left ventricle while it was 89 mm. systolic in the aorta. The aortic leaflets were normal. Diffuse muscular hypertrophy of the outflow tract of the left ventricle was noted about 1 cm. upstream from the aortic leaflets without any evidence of a localized fibrous or muscular ring. A 2-inch incision was made in the free wall of the left ventricle. Through this incision the obstructing muscular mass was excised. In the operating room after repair, pressure in the cavity of the left ventricle was 82 mm. systolic while that in the root of the aorta was 78 mm. systolic. Postoperative convalescence was uneventful.

The patient returned to the clinic for reexamination on March 11, 1960. He had been entirely well since his operation and had resumed full activity including strenuous farm work without symptoms. No longer did he experience angina,

dyspnea, or undue fatigue. On physical examination no murmur was heard in the aortic area but a faint systolic murmur, grade I, was heard in the fourth left interspace and at the apex. He had gained 30 pounds. A roentgenogram of the thorax showed a slight decrease in the size of the cardiac silhouette. No change was apparent on the electrocardiogram. The patient's postoperative result was considered excellent.

Case 2

A 20-year-old white woman presented with a history of exertional dyspnea and fatigue with occasional episodes of paroxysmal nocturnal dyspnea since the age of 11. Symptoms had been more marked in the year prior to admission. On physical examination the blood pressure was 124 mm. of mercury systolic and 76 mm. diastolic. A grade-I systolic murmur, which became grade III with exercise, was heard in the aortic region. The murmur was heard only faintly in the neck. A roentgenogram of the thorax revealed evidence of cardiac enlargement and the electrocardiogram revealed advanced left ventricular hypertrophy. Pressures were recorded at 216 mm. systolic and 8 mm. diastolic in the cavity of the left ventricle and 81 mm. systolic and 51 mm. diastolic in the radial artery by the percutaneous puncture technic.

Operation was accomplished on September 13, 1960. The appearance of the left ventricle was striking. Massive hypertrophy prevailed, the ventricle being so large and firm that it seemed almost to be a solid nonbeating tumor. Leaflets of the aortic valve were normal. No localized obstruction was found immediately beneath the valve, but about 1 cm. upstream from the base of the valve was a greatly hypertrophied mass of muscle, which was particularly large along the septal side of the aortic outflow tract. Most of this mass, and particularly that along the septal side, was excised through a 3-cm. incision in the left ventricle. After closure of the aortotomy the aortic clamp was removed and the heart became hard in ventricular fibrillation. Palpation of the region of resection through the left ventriculotomy now revealed no obstruction. The ventriculotomy was closed. After the heart had again taken over the circulation, pressure in the cavity of the left ventricle was 108 mm. systolic and 12 mm. diastolic, while that in the left arm by the cuff method was 105 mm. systolic.

Convalescence was uneventful. On the eleventh postoperative day a needle was passed percutaneously into the cavity of the left ventricle where the pressure was recorded at 100 mm. systolic. Unfortunately a needle could not be passed into the brachial artery, but the pressure in the right arm was 115 mm. systolic by the cuff method.

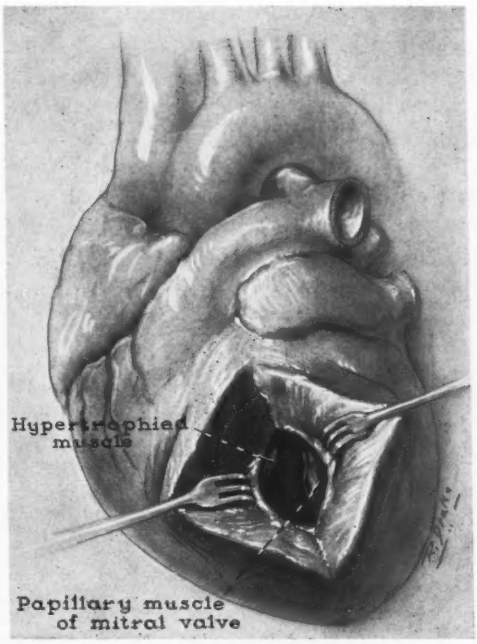

Figure 3

Surgical exposure through left ventriculotomy incision. The chordae and papillary muscle of the mitral valve must be visualized and protected during resection of the hypertrophied muscle forming the obstruction. In actual practice the surgeon's index finger is passed through the aortotomy (not shown) to protect by palpation the aortic valve leaflets during resection.

Discussion

Brock,[1] in 1957, first referred to the diffuse, acquired subvalvular aortic obstruction observed in patients with systemic artery hypertension. Brachfeld and Gorlin[2] found that such diffuse muscular subvalvular aortic stenosis could be idiopathic, rather than secondary, in some patients. Morrow and Braunwald[3] reported two such cases, and stated that in neither was the lesion amenable to surgical correction. They properly directed attention to the fact that this entity should be suspected when operating for congenital aortic stenosis in a patient who, at operation, is shown to have neither valvular stenosis nor a localized subvalvular obstruction.

Although the technic described herein has been used in only two cases as yet, it would seem applicable generally to patients with this uncommon type of subaortic obstruction. Data available in these two cases seem sufficient to indicate that effective relief of the subaortic obstruction has been obtained.

Concern must be had for the placement of an incision in the wall of the left ventricle. In neither of these patients, however, was there evidence of undue reduction of cardiac output after operation, nor have there been any late ill effects that could be attributed to the left ventriculotomy.

Summary

Direct surgical relief of diffuse subvalvular aortic stenosis has been accomplished in two cases by open operation through a left ventriculotomy.

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When Harvey's discovery, like an earthquake, had broken up galenism and other outworn sophistries, his masterly work stood forth against a more lurid background of folk superstitions—of vampires, witch-burning, magic, cabbalism, astrology, alchemy, chiromancy, and water-casting. In physics, terrestrial and celestial, Galileo, persecuted as he was, had some current with him and before him; Copernicus had preceded him, Kepler was beside him: but in physiology the waters had closed upon the path of Galen as upon the wake of a great ship; the anatomists, themselves galenists, had given Harvey little help; and the share of Servetus, Colombo, and Fabricius was but small in the discovery of the central fact of the science, and of the method which opened the way to Pecquet and Aselli, to Glisson, to Steno, to Wharton and Willis, to Haller and Bernard. Harvey's discovery was the first step to a transfiguration of medicine; and though after Harvey there arose much false physiology and therewith again great floods of medical sophistry, yet from his time medicine has had to reckon with physiology, the only source of scientific nosology and therapeutics.—THOMAS CLIFFORD, ALLBUTT, M.A., M.D. *Science and Medieval Thought.* London, C. J. Clay & Sons, 1901, p. 111.

Body Fluid and Electrolyte Composition in Cardiac Patients with Severe Heart Disease but without Peripheral Edema

By A. V. CHOBANIAN, M.D., B. A. BURROWS, M.D., AND W. HOLLANDER, M.D.

ALTHOUGH excessive retention of sodium and water is a striking feature in frank congestive heart failure, little is known about the abnormalities in body fluid and electrolyte metabolism in cardiac patients with severe heart disease prior to the development of obvious peripheral edema. Previous studies in nonedematous cardiac patients have not revealed any impairment in the handling of oral or intravenous sodium loads prior to the appearance of edema.[2, 3] Therefore, the present study was undertaken to determine whether any abnormality in body fluid and electrolyte metabolism might be present in such patients even though they might appear to handle sodium loads normally. When it was found that these nonedematous cardiac patients had significant increases in exchangeable sodium and radiosulfate space, it was decided to attempt to correlate such changes in body fluids and electrolytes with cardiovascular and renal hemodynamic function.

From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.

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Work done in part during tenure (Dr. Chobanian) of Postdoctoral Research Fellow of the National Heart Institute.

Dr. Hollander is a Special Research Fellow, National Institutes of Health.

A portion of the present data was presented at the Thirtieth Scientific Sessions of the American Heart Association, Chicago, Illinois, October 1957, and appeared in abstract form.[1]

Clinical Material and Methods

Thirty-one ambulatory cardiac patients with severe heart disease but without peripheral edema were included in the study. All had dyspnea on exertion and limitation of physical activity, but none gave a history or had clinical evidence of peripheral edema. All patients had eaten a diet unrestricted in salt and had not received any diuretic agents for at least 2 weeks prior to the performance of these studies. The heart disease was secondary to rheumatic valvular involvement in 14 of the patients, hypertensive disease in seven, atherosclerotic disease in four, and congenital defects in six. One of the patients with atherosclerotic heart disease had an associated isolated adrenal defect in mineralocorticoid production and has been reported in detail elsewhere.[4] Cardiac enlargement was evident in all patients by either electrocardiographic or roentgenographic examination. Twelve of the patients were taking maintenance doses of digitalis during the period of study. The blood urea nitrogen level was within normal limits in all but one patient, who had renal insufficiency secondary to chronic pyelonephritis.

Measurements of exchangeable sodium (Na^{24} space, or Na_e), exchangeable potassium (K^{42} space, or K_e), extracellular fluid volume ($S^{35}O_4$ space, or ECF), serum sodium (Na_s), serum potassium (K_s), and serum osmolality (ser. osm.) were made in all cardiac patients and in normal ambulatory controls (hospital employees) who were matched in age, sex, weight, and body build. The measurements were made according to methods previously reported from this laboratory.[5] Tracer doses of radioactive sodium (Na^{24}) and radioactive potassium (K^{42}) were administered orally and following a 22- to 24-hour period of equilibration, determinations of serum and urine specific activities were made to calculate exchangeable sodium and potassium. Duplicate samples were analyzed for Na^{24} and K^{42} activity with a well-type sodium iodide and plastic phosphor scintillation counter. The radiosulfate space was measured 20 minutes following the intravenous administration of a tracer dose of radiosulfate. Serum and

Table 1A

Cardiac Patients with Elevated Mean Pulmonary "Capillary" Pressures

Subject	Sex	Age, yr.	Clinical classification	BP mm. Hg	Body wt. Kg.	SA M^2	Serum osm. mOsm./L.	ECF ($S^{35}O_4$ space) % body wt.	Na_e mEq./L.	K_e mEq./L.	Na_e/body wt. mEq./Kg.	K_e/body wt. mEq./Kg.
T.Z.	F	51	RHD MI, MS II C	120/60	57.7	1.59	284	19.4	140	4.0	48.8	30.0
E.C.	F	55	RHD MS III C	105/60	47.3	1.51	291	18.1	147	4.7	53.7	33.1
C.P.	F	23	RHD MI II C	145/80	42.3	1.38	282	19.1	138	4.0	58.7	32.1
T.C.	M	50	ASHD II B	105/60	57.6	1.64	287	18.1	145	4.6	41.1	36.9
A.J.	M	60	ASHD II B	140/75	50.0	1.64	327	20.4	141	4.7	63.1	29.0
M.D.	F	55	HCVD II B	220/125	46.8	1.44	285	21.1	139	3.7	48.5	35.1
E.G.	M	58	HCVD II B	205/125	61.4	1.72	280	17.0	139	4.1	51.5	34.7
M.S.	F	55	HCVD III C	210/130	45.7	1.40	325	18.1	142	5.1	50.5	34.4
R.C.	M	53	HCVD II B	195/115	61.9	1.70	289	20.2	141	3.3	50.9	36.0
E.W.	F	46	HCVD III C	215/135	46.4	1.51	287	26.1	141	3.7	62.5	35.5
M.C.	F	29	RHD MS II B	120/70	61.6	1.71	294	13.0	146	5.1	36.9	33.3
C.M.	F	45	RHD MS II B	125/85	50.0	1.51	286	17.1	141	4.6	41.1	27.8
M.S.	F	61	RHD MI, MS III C	120/75	58.2	1.65	290	17.0	140	4.2	47.2	28.5

Key to Abbreviations:

RHD, rheumatic heart disease; HCVD, hypertensive cardiovascular disease; ASHD, atherosclerotic heart disease; MI, mitral insufficiency; MS, mitral stenosis; I-IV, functional capacity grading; A-E, therapeutic classification grading.

urine samples were obtained and analyzed for S^{35} radioactivity with a thin-window Geiger-Mueller tube. Sodium and potassium were measured in urine and plasma with an internal standard (lithium) flame photometer. Serum osmolality was determined by freezing point depression with a Fiske osmometer.

In seven of these patients selected on the basis of demonstrable increases in exchangeable sodium and extracellular fluid volume, the radioisotope dilution studies were repeated following a 7- to 14-day period when dietary sodium was controlled at 180 mEq. daily and again following a 7- to 14-day period when dietary sodium was restricted to 9 mEq. daily and either chlorothiazide or meralluride was administered. Body weight was measured daily and the patients were observed closely for clinical changes during these periods. In two other patients with elevation of exchangeable sodium, changes in body sodium con-

Table 1A (continued)

Cardiac Patients with Elevated Mean Pulmonary "Capillary" Pressures

Subject	Sex	Age, yr.	Clinical classification	BP mm. Hg	Body wt. Kg.	SA M^2	Serum osm. mOsm./L.	ECF ($S^{35}O_4$ space) % body wt.	Na_e mEq./L.	K_e mEq./L.	Na_e/body wt. mEq./Kg.	K_e/body wt. mEq./Kg.
D.B.	F	42	RHD MS II C	130/70	53.4	1.52	297	18.2	139	5.0	38.4	32.9
A.F.	M	47	RHD MI II B	120/60	60.9	1.79	289	20.6	141	4.2	46.2	47.0
C.D.	F	48	RHD MS II B	105/55	54.1	1.56	294	16.7	142	4.0	44.0	37.2
Y.G.	F	55	RHD MS II C	105/70	45.5	1.43	292	16.7	132	3.8	45.5	42.6
W.L.	F	49	RHD MI, MS II B	100/55	38.4	1.26	283	15.9	139	4.5	41.3	28.0
T.H.	F	57	RHD MI III C	110/65	60.9	1.70	293	18.2	140	4.2	47.2	28.5
R.W.	M	63	HCVD II C	185/125	88.6	2.11	303	16.8	142	3.7	46.8	26.5
Y.D.	F	44	RHD MS II B	120/75	54.9	1.56	286	14.9	140	3.4	38.8	24.0
E.H.	M	51	HCVD III C	175/110	51.8	1.61	285	20.9	141	3.6	49.4	36.0
S.L.	F	43	HCVD II B	245/150	39.5	1.35	271	20.2	134	4.0	45.0	35.6
G.N.	M	72	ASHD I° Hypoaldosteronism II C	230/85	52.3	1.55	285	17.8	137	4.9	47.1	33.1
S.L.	F	30	RHD MI, MS II B	100/60	54.0	1.50	296	15.8	141	4.2	43.7	35.5

Key to Abbreviations:

RHD, rheumatic heart disease; HCVD, hypertensive cardiovascular disease; ASHD, atherosclerotic heart disease; MI, mitral insufficiency; MS, mitral stenosis; I-IV, functional capacity grading; A-E, therapeutic classification grading.

tent were also measured by means of metabolic balance technics during a 7-day control period when dietary sodium intake was maintained at 180 mEq. daily and then during a subsequent 10-day period when dietary sodium was restricted to 9 mEq. daily and chlorothiazide was administered in a daily oral dosage of 1.0 Gm. The dietary intake of sodium was controlled by adding measured amounts of sodium to a 9-mEq. daily sodium intake. The daily net balance of sodium was measured as the difference between the dietary intake and the urinary excretion of sodium. All metabolic studies were carried out on an ambulatory basis. All meals were prepared by the dietary kitchen and none of the patients was hospitalized or advised to restrict his activities.

Venous catheterization of the heart was performed in 23 of the cardiac patients according to previously described methods.[2] All catheterization studies were made in the postabsorptive state

Table 1B

Control Subjects

Subject	Sex	Age, yr.	Clinical classification	BP mm. Hg	Body wt. Kg.	SA M^2	Serum osm. mOsm./L.	ECF (SO_4 space) % body wt.	Na_e mEq./L.	K_e mEq./L.	Na_e/body wt. mEq./Kg.	K_e/body wt. mEq./Kg.
A.J.	F	43	Normal	100/65	66.3	1.65	288	16.1	143	3.8	37.8	34.7
R.T.	F	56	Normal	115/75	47.5	1.50	288	16.0	142	4.4	36.9	43.1
A.A.	F	32	Normal	105/65	39.9	1.41	289	14.4	140	4.7	41.3	42.0
L.C.	M	55	Normal	135/75	54.8	1.63	292	13.7	141	3.9	39.8	37.6
R.S.	M	58	Normal	115/80	48.6	1.40	292	14.7	139	4.2	41.6	35.8
R.K.	F	58	Normal	105/70	48.3	1.45	292	12.3	139	4.0	41.6	34.1
K.C.	M	61	Normal	155/60	57.5	1.67	291	12.8	143	3.8	36.7	32.5
N.W.	F	57	Normal	140/70	47.0	1.40	295	15.1	138	4.7	39.8	38.6
I.F.	M	54	Normal	130/75	61.4	1.71	291	15.3	142	4.6	44.6	39.8
T.R.	F	50	Normal	120/90	49.4	1.53	290	14.1	142	4.2	38.8	41.4
F.W.	F	25	Normal	125/85	62.5	1.73	290	14.9	140	4.3	39.1	42.4
S.R.	F	45	Normal	125/75	49.5	1.50	289	17.0	140	4.2	36.7	43.2
G.H.	F	56	Normal	125/80	66.1	1.69	284	14.8	143	4.1	34.5	32.4
S.M.	F	37	Normal	120/75	50.9	1.55	291	11.2	141	4.0	32.5	32.2
E.H.	M	48	Normal	125/80	66.6	1.75	288	14.0	140	4.3	42.0	40.5
M.M.	F	41	Normal	115/75	52.0	1.51	277	14.3	137	3.6	34.8	33.4
M.A.	F	60	Normal	100/60	42.0	1.38	291	14.2	139	4.3	41.4	36.6
A.L.	F	50	Normal	115/75	37.5	1.31	287	15.1	138	3.9	39.0	40.4
E.P.	F	53	Normal	130/80	58.6	1.65	288	16.0	141	5.3	32.5	29.9
S.P.	M	62	Normal	125/85	85.0	1.95	288	16.5	140	4.4	35.6	32.8
S.A.	F	40	Normal	115/70	52.8	1.58	290	13.1	142	4.8	39.2	40.0
J.W.	M	49	Normal	120/70	55.9	1.68	293	16.2	140	3.7	42.5	34.2
M.C.	F	42	Normal	120/85	40.3	1.41	289	13.7	137	4.9	38.5	40.7
L.M.	M	68	Normal	150/65	50.6	1.60	294	13.6	142	4.6	41.0	38.9
B.B.	F	32	Normal	120/80	51.5	1.56	296	15.0	141	4.3	36.7	44.3

without sedation. A double-lumen cardiac catheter was used to measure pressures in the right atrium, right ventricle, pulmonary artery, and pulmonary "capillary" areas. Resting cardiac output determinations were made by the direct Fick method. Expired air was collected for 2 minutes in a Douglas bag, and simultaneous blood samples were obtained from the brachial and pulmonary arteries. The volume of inspired air was measured by a Tissot spirometer and oxygen concentrations in the expired air were determined with either the Haldane or Scholander apparatus. Blood samples were analyzed for oxygen content, capacity, and saturation by the Van Slyke manometric apparatus.

In 15 of the patients studied by cardiac catheterization, measurements of inulin and para-aminohippurate clearances were also made according to previously described methods.[2] An indwelling catheter was placed in the urinary bladder and, after standard priming doses, a steady infusion of inulin and para-aminohippurate was administered at a constant rate by means of a calibrated drip. Three to four urine collections were made at 15-minute intervals by washing out the bladder with distilled water and evacuating the residual urine by displacement with air. Arterial blood samples were obtained for the determination of inulin and para-aminohippuric acid. Blood and urine concentration of para-aminohippurate and inulin were measured by the standard methods of Goldring and Chasis, and Schreiner respectively.

All cardiac catheterizations and renal clearance measurements were made within 1 to 14 days of the radioisotope space determinations.

Results

The results in the cardiac patients with increased pulmonary "capillary" pressures and their normal controls are summarized in tables 1-4. The results in the patients with normal pulmonary "capillary" pressures and their normal controls are summarized separately in tables 5 and 6. The statistical analyses of these findings are given in table 7.

Table 2

Hemodynamic Data in Cardiac Patients with Elevated Mean Pulmonary "Capillary" Pressures

Subject	Cardiac index (L./min./M.²)	Pressures (mm. Hg) Pulmonary artery S	D	M	Mean pulmonary "capillary"	Right ventricle S	D	Right atrium	C_{PAH} (ml./min./1.73M.²)	C_{IN} (ml./min./1.73M.²)
T.Z.	2.5	38	20	27	15	36	4	4	443	119
E.C.	2.5	51	28	35	19	50	8	7	290	93
C.P.	2.4	48	20	35	18	50	8	7	472	110
T.C.	3.9	32	20	24	15	32	6	6	343	91
A.J.	3.3	42	32	36	24	40	5	6	272	78
M.D.	4.5	36	21	26	14	37	3	4	244	95
E.G.	3.7	34	19	24	14	34	4	4	387	102
M.S.	4.1	55	32	39	24	53	8	7	92	24
R.C.	2.4	74	37	49	29	71	9	9	212	91
E.W.	2.2	59	38	46	25	59	5	4	243	76
M.C.	3.3	40	26	31	20	38	3	3	474	127
C.M.	2.5	38	23	28	18	38	3	2	334	112
M.S.	2.2	55	30	38	25	53	8	7	242	113
D.B.	2.1	55	33	38	18	55	5	5	264	96
A.F.	3.2	53	30	37	25	53	5	5	282	98
C.D.	4.4	34	19	24	13	32	1	1	...	...
Y.G.	2.5	42	29	33	22	40	4	4	...	...

Key to Abbreviations:

L, liters; M.², square meters of surface area; S, systolic; D, diastolic; M, mean; C_{PAH}, clearance of para-aminohippurate; C_{IN}, clearance of inulin.

Serum Electrolytes and Osmolality

Serum sodium concentrations were not significantly different in either of the cardiac groups from those in the normal controls who were matched according to age, sex, weight, and body build. No significant changes in serum sodium were noted when the patients were maintained on a daily sodium intake of 180 mEq., although slight reductions in serum sodium ranging from 1 to 5 mEq. per liter were observed when their dietary sodium was restricted to 9 mEq. daily and when they were given diuretic agents.

Serum potassium in both cardiac groups did not differ significantly from the normal groups and did not change significantly during the 180-mEq. sodium intake or following sodium restriction and diuretic therapy.

Serum osmolality showed no significant differences from normal in either cardiac group and did not change significantly during the controlled 180-mEq. sodium intake. Insignificant reductions in serum osmolality ranging from 1 to 9 mOsm. per liter were observed following sodium restriction and diuretic administration.

Extracellular Fluid Volume

The radiosulfate space was significantly increased in the cardiac group that had increased mean pulmonary "capillary" pressure. No significant elevations in sulfate space or in body weight were observed when the seven selected cardiac patients were maintained on a 180-mEq. sodium intake. Sodium restriction and diuretic therapy produced a mean reduction in radiosulfate space of 0.9 liters and a mean decrease in body weight of 1.2 Kg.; however, even after this therapy the extracellular fluid volume appeared elevated above normal, with a mean value of 18.8 per cent body weight. In the patients with congenital heart disease who had normal pulmonary "capillary" pressure, the sulfate space did not differ significantly from the normal controls.

Exchangeable Sodium

Exchangeable sodium was significantly increased in the cardiac group that had increased pulmonary capillary pressures. The percentage increase in Na_e was 23 per cent above normal levels as compared to an increase in sulfate space of 25 per cent. No sig-

Table 3

Effects of Dietary Sodium Intake and Diuretic Agents in Cardiac Patients without Peripheral Edema

Patient	Daily Na intake	Duration (days)	Body wt. (Kg.)	Serum osm. (mOsm./L.)	ECF (Liters)	Na_e (mEq./L.)	K_e (mEq./L.)	Na_e (mEq.)	K_e (mEq.)
T.Z.	Unrestricted	14	57.7	284	11.2	140	4.0	2815	1730
	180 mEq.	10	59.5	284	11.5	141	3.8	2839	1697
	9 mEq. (chlorothiazide 1.0 Gm./day)	10	56.4	280	10.8	139	3.4	2621	1705
E.C.	Unrestricted	14	47.3	291	8.45	147	4.7	2541	1565
	180 mEq.	7	47.5	293	8.37	145	4.9	2601	1721
	9 mEq. (meralluride 2.0 ml. I.M. × 6)	14	46.6	289	6.85	140	3.5	2404	1796
C.P.	Unrestricted	14	43.2	282	8.06	138	4.0	2484	1358
	180 mEq.	7	42.3	282	9.47	140	4.0	2308	1438
	9 mEq. (meralluride 2.0 ml. I.M. × 4)	14	41.4	281	7.20	138	3.7	2234	1417
A.J.	Unrestricted	14	50.0	297	8.65	141	4.7	3201	1469
	180 mEq.	14	50.7	294	8.52	143	4.6	3119	1655
	9 mEq. (chlorothiazide 1.0 Gm./day)	7	48.7	293	7.72	141	5.3	2661	1630
E.W.	Unrestricted	14	46.4	287	12.7	141	3.7	2900	1648
	180 mEq.	7	46.5	290	12.4	138	4.1	3001	1707
	9 mEq. (meralluride 2.0 ml. I.M. × 2)	7	45.0	281	12.1	140	3.8	2723	1737
Y.G.	Unrestricted	14	45.5	290	7.60	136	3.7	2070	1942
	180 mEq.	10	45.4	289	7.43	137	3.9	2274	2038
	9 mEq. (chlorothiazide 1.0 Gm./day)	10	45.0	287	6.91	132	3.8	2052	1836
R.C.	Unrestricted	14	61.9	289	12.5	141	3.3	3151	2229
	180 mEq.	7	62.1	292	13.1	139	3.4	3099	2107
	9 mEq. (chlorothiazide 1.0 Gm./day)	14	60.8	287	12.8	136	3.1	3051	1759

Table 4

Effects of Dietary Sodium and Diuretic Agents on the Metabolic Sodium Balance in Cardiac Patients without Peripheral Edema

Patient	Daily Na intake	Duration (days)	Body Wt. (Kg.)	ΔNa Balance (mEq.)	Na_e/Body Wt. (mEq./Kg.)
M.D.	Unrestricted	14	46.8	—	48.5
	180 mEq.	7	46.7	+ 64	—
	9 mEq. (chlorothiazide 1.0 Gm./day)	10	45.9	−174	—
M.S.	Unrestricted	14	58.2	—	47.2
	180 mEq.	7	58.3	− 12	—
	9 mEq. (chlorothiazide 1.0 Gm./day)	10	57.0	−206	—

Table 5A

Cardiac Patients with Normal Mean Pulmonary Capillary Pressures

Subject	Sex	Age, yr.	Clinical classification	BP mm. Hg	Body wt. Kg.	SA M^2	Serum osm. mOsm./L.	ECF ($S^{35}O_4$ space) % body wt.	Na_e mEq./L.	K_e mEq./L.	Na_e/body wt. mEq./Kg.	K_e/body wt. mEq./Kg.
A.P.	F	45	Eisenmenger III C	105/55	45.2	1.40	288	16.7	141	4.7	46.9	34.3
R.B.	F	40	PDA II B	100/60	66.8	1.72	292	14.3	135	4.2	38.3	32.8
J.K.	F	28	ASD II B	110/70	56.8	1.63	286	13.1	137	4.3	27.2	42.5
J.A.	M	25	PS II B	125/75	54.3	1.68	290	18.1	137	4.4	40.2	41.4
F.B.	M	52	PS ASD II C	105/60	60.2	1.76	291	11.4	137	4.8	35.2	34.5
F.H.	F	34	PS VSD II B	125/70	56.1	1.58	284	13.9	144	4.1	35.2	37.6

Key to Abbreviations:

PDA, patent ductus arteriosus; ASD, atrial septal defect; VSD, ventricular septal defect; PS, pulmonic stenosis.

Table 5B

Normal Controls

Subject	Sex	Age, yr.	Clinical classification	BP mm. Hg	Body wt. Kg.	SA M^2	Serum osm. mOsm./L.	ECF ($S^{35}O_4$ space) % body wt.	Na_e mEq./L.	K_e mEq./L.	Na_e/body wt. mEq./Kg.	K_e/body wt. mEq./Kg.
M.C.	F	42	Normal	120/85	40.3	1.41	289	13.7	137	4.9	38.5	40.7
A.J.	F	43	Normal	100/65	66.3	1.65	288	16.1	143	3.8	37.8	34.7
B.B.	F	32	Normal	120/80	51.5	1.56	296	15.0	141	4.3	36.7	44.3
R.Q.	M	30	Normal	110/75	58.6	1.72	287	14.0	138	4.5	36.1	33.2
I.F.	M	54	Normal	130/75	61.4	1.71	291	15.3	142	4.6	44.6	39.8
S.A.	F	40	Normal	115/70	52.8	1.58	290	13.1	142	4.8	39.2	40.0

nificant increase in exchangeable sodium was observed when the patients were maintained on a 180-mEq. sodium intake. With dietary sodium restriction and diuretic therapy, all patients showed some reduction in Na_e ranging from 48 to 358 mEq. but Na_e remained elevated above normal levels. Even though body sodium remained elevated, two of the patients had symptoms and signs of sodium deficiency with marked weakness, tachycardia, and narrowed arterial pulse pressure. Exchangeable sodium showed no significant increase in the group with congenital heart disease with normal pulmonary "capillary" pressures.

Exchangeable Potassium

Exchangeable potassium showed a slight but significant decrease below control levels in the cardiac patients. No significant changes in K_e were noted when the patients were maintained either on a 180-mEq. sodium intake or a 9-mEq. sodium intake with diuretic administration. Exchangeable potassium did not differ significantly from normal in the congenital cardiac group with normal pulmonary "capillary" pressures.

Metabolic Sodium Balance

In the two patients in whom metabolic balances were performed, exchangeable sodium was elevated above the normal range during

Table 6

Hemodynamic Data in Cardiac Patients with Normal Mean Pulmonary "Capillary" Pressures

Subject	Cardiac index (L./min./M.²)	Pressures (mm. Hg) Pulmonary artery S	D	M	Mean pulmonary "capillary"	Right ventricle S	D	Right atrium
A.P.	3.7	105	55	73	8	102	7	7
R.B.	3.3	65	30	44	10	64	5	3
J.K.	2.7	80	42	55	6	82	3	3
J.A.	4.5	15	10	12	8	80	1	1
F.B.	2.8	18	11	15	8	70	4	3
F.H.	2.5	16	16	13	7	66	5	4

the control period. Following 10 days of controlled sodium intake at 180 mEq. daily, no appreciable changes in sodium balance were observed, with a net increase in the cumulative sodium balance of 64 mEq. in one and a net decrease of 12 mEq. in the other of the two patients studied. During the 10 days of sodium restriction and diuretic therapy there were net decreases in cumulative sodium balance of 174 and 206 mEq. respectively.

Hemodynamic Functions

The cardiac index in the patients with acquired heart disease averaged 3.0 L./min./M.² Nine of the 17 patients studied with acquired heart disease had a cardiac index below 2.8, but in the remaining eight patients the cardiac index was in the normal range.

In the group with congenital heart disease, the cardiac index averaged 3.3 L./min./M.² Two of the six patients had a cardiac index below 2.8 ml./min./M.²

The right ventricular end-diastolic pressure averaged 5 mm. Hg. In 11 members of this group the right ventricular filling pressure was below 6 mm. Hg.

In the group with congenital heart disease the right ventricular end-diastolic pressure averaged 4 mm. Hg and ranged from 1 to 7 mm. Hg. As in the group with acquired heart disease, none of the patients had increases in filling pressure of greater than 10 mm. Hg, and in five of the patients the end-diastolic pressure was less than 6 mm. Hg.

Right ventricular systolic pressure was elevated above 30 mm. Hg in all patients with either acquired or congenital heart disease.

All the patients studied with acquired heart disease had mild to moderate pulmonary hypertension. In the congenital heart group three patients with pulmonic stenosis had normal pulmonary artery pressures and the remaining three had increases.

The mean pulmonary "capillary" pressure was elevated in all patients with acquired heart disease. In contrast to this group, the mean pulmonary "capillary" pressure was in the normal range in all subjects with congenital heart disease, with a mean of 8 and range of 6 to 10 mm. Hg.

The glomerular filtration rate averaged 95 ml./min./M.² in the patients with acquired heart disease. In five of these patients, the glomerular filtration rate appeared to be within normal limits with values greater than 110 ml./min./1.73 M.²

The renal plasma flow averaged 307 ml./min./1.73 M.² being reduced below the normal range with all values below 475 ml./min./1.73 M.²

Discussion

These studies demonstrate that subclinical retention of sodium and water may be present in selected cardiac patients before the development of obvious edema. Similar increases in exchangeable sodium have previously been reported in nonedematous animals with experimentally produced valvular lesions,[6] while increases in extracellular fluid volume have been noted in nonedematous human cardiac patients.[7]

Unlike cardiac patients with peripheral edema, the patients reported in this study

Table 7

Mean Data and Statistical Analysis

	Age	Body wt. Kg.	SA M^2	Ser. osm. mOsm./L.	ECF ($S^{35}O_4$ space) % body wt.	Na_e mEq./L.	K_e mEq./L.	Na_e/body wt. mEq./Kg.	K_e/body wt. mEq./Kg.
Cardiac patients with increased pulmonary "capillary" pressures vs. normal controls									
Control	49.3 ± 2.1*	53.7 ± 2.1	1.57 ± .03	290 ± 0.8	14.6 ± 0.3	140 ± 0.4	4.3 ± 0.1	38.6 ± 0.6	37.7 ± 0.8
Cardiac subjects	49.7 ± 2.2*	53.6 ± 2.0	1.57 ± .03	291 ± 2.5	18.3 ± 0.5	140 ± 0.6	4.2 ± 0.1	47.5 ± 1.4	33.3 ± 1.0
Mean difference	0.4 ± 3.1†	—0.1 ± 2.9	0 ± .04	1.5 ± 2.6	3.7 ± 0.6	—0.1 ± 0.7	—0.1 ± 0.1	8.9 ± 1.5	—4.4 ± 1.3
P	0.9	>0.9	0.9	0.6	<0.01	0.9	0.6	<0.01	<0.01
Cardiac patients with normal pulmonary "capillary" pressures vs. normal controls									
Control	40.2 ± 3.5	55.1 ± 3.7	1.61 ± 0.05	290 ± 1.3	14.5 ± 0.5	141 ± 1.0	4.5 ± 0.2	38.8 ± 1.2	38.8 ± 1.7
Cardiac subjects	37.3 ± 4.2	56.5 ± 2.9	1.63 ± 0.05	288 ± 1.3	14.6 ± 1.0	139 ± 1.4	4.4 ± 0.1	37.2 ± 2.7	37.2 ± 1.6
Mean difference	—2.9 ± 5.5	1.4 ± 4.7	0.02 ± 0.07	—1.7 ± 1.8	0.1 ± 1.1	—2.0 ± 1.7	—0.1 ± 0.2	—1.6 ± 2.9	—1.6 ± 2.3
P	0.6	0.8	0.8	0.4	>0.9	0.3	0.7	0.6	0.5

	Body wt. Kg.	Ser. osm. mOsm./L.	ECF L	Na_e mEq./L.	K_e mEq./L.	Na_e mEq.	K_e mEq.
Effects of 180 mEq. Na intake in cardiac patients with increased pulmonary "capillary" pressure							
Unrestricted diet	50.3 ± 2.6	289 ± 1.9	9.9 ± 0.8	140 ± 1.3	4.0 ± 0.2	2737 ± 152	1706 ± 112
180 mEq./day Na intake	50.3 ± 2.7	289 ± 1.7	10.1 ± 0.8	140 ± 1.1	4.1 ± 0.2	2749 ± 136	1766 ± 87
Mean difference	0 ± 3.7	0 ± 0.6	0.2 ± 1.2	—0.2 ± 1.7	0.1 ± 0.3	11 ± 204	60 ± 142
P	>0.9	0.8	0.9	>0.9	0.8	>0.9	0.7
Effects of dietary Na restriction and diuretics in cardiac patients with increased pulmonary "capillary" pressures							
180 mEq./day Na intake	50.3 ± 2.7	289 ± 1.7	10.1 ± 0.8	140 ± 1.1	4.1 ± 0.2	2749 ± 136	1766 ± 87
9 mEq./day and diuretics	49.1 ± 2.6	285 ± 1.9	9.2 ± 1.0	138 ± 1.1	3.8 ± 0.3	2535 ± 126	1697 ± 53
Mean difference	—1.2 ± 3.7	—3.7 ± 2.6	—0.9 ± 1.2	—2.6 ± 1.7	—0.3 ± 0.3	—214 ± 185	—69 ± 102
P	0.8	0.3	0.5	0.2	0.4	0.3	0.5

*Mean ± standard error.

†Mean difference ± standard error of the difference of the mean.

were able to tolerate moderately high dietary sodium intakes without developing either clinically detectable peripheral edema, or increases in the severity of cardiac symptoms, body sodium balance, or extracellular fluid volume. The increases in exchangeable sodium and extracellular fluid volume in these patients were not corrected to normal levels by dietary sodium restriction and the administration of diuretic agents. During such therapy some of the patients actually had symptoms and signs of sodium depletion even though exchangeable sodium remained elevated above control levels. These observations suggest that these patients are capable of handling high-salt intakes in a normal manner but that they do so at a new equilibrium state of increased body sodium and expanded extracellular fluid volume. This ability to tolerate sodium loads in the face of an increase in body sodium and extracellular fluid volume is similar to the findings observed in nonedematous patients with malignant hypertension and primary hyperaldosteronism[5, 8] and in edematous patients with the nephrotic syndrome.[9]

The primary mechanisms involved in the renal retention of sodium in congestive heart failure have not been clearly established as yet. In advanced congestive failure, multiple factors such as increased venous pressure, reduced glomerular filtration rate and renal plasma flow, increased aldosterone secretion and increased tubular reabsorption of sodium all may contribute to the observed abnormalities in sodium and water metabolism. But the role of any one of these factors as the primary cause for sodium retention is uncertain. In animals with mild heart failure secondary to experimentally produced valvular lesions, and in man with congestive failure, alterations in renal sodium excretion have been observed without measureable changes in venous pressure or glomerular filtration rate.[10, 11] With regard to aldosterone, increased rates of aldosterone secretion have been observed to play an important early role in renal sodium retention in experimentally induced heart failure[12] but a similar role in man is not clearly evident in view of the reported observations that not all patients with heart failure (even in the presence of peripheral edema) show increases in aldosterone secretion.[13]

Since aldosterone secretion or excretion were not measured in these subjects, the possible role of aldosterone cannot be clearly defined from this investigation. One of the patients included in this study, however, was a man with primary hypoaldosteronism who had an increase in exchangeable sodium and extracellular fluid volume comparable to that observed in the other patients studied, even though he had a unique isolated adrenal defect in mineralocorticoid production. Furthermore, although these cardiac patients had significant increases in exchangeable sodium and extracellular fluid volume corresponding in degree to that observed in patients with primary hyperaldosteronism previously studied in this laboratory, the degree of body potassium depletion was much less than that seen in those patients with documented mineralocorticoid excess.[8]

The present studies suggest that abnormalities in venous pressure, cardiac output, or glomerular filtration rate need not necessarily precede the observed increase in body salt and water retention and therefore may not play a primary role in the early stages of sodium retention. Decreases in renal plasma flow were found in all the cardiac patients who had increases in exchangeable sodium and extracellular fluid volume and cannot be ruled out as an important initial factor in the renal retention of sodium. It is noteworthy, however, that patients with uncomplicated arterial hypertension who also have decreases in renal plasma flow do not have increases in exchangeable sodium and extracellular fluid volume. Increases in exchangeable sodium and extracellular fluid volume were always accompanied by increases in pulmonary "capillary" pressure but were absent in the patients with congenital heart disease who were studied, even when the pulmonary artery pressure alone was elevated. These findings suggest that stimulation of pressure sensitive receptors in the pulmonary veins or the left atrium may play a role in initiating changes

in renal salt and water excretion. Actual neuroreceptors have been demonstrated anatomically in the pulmonary vein and left atrial wall[14] and have been implicated previously by the effects of positive- and negative-pressure breathing on urine flow.[15]

Summary and Conclusions

Nonedematous cardiac patients with severe heart disease may exhibit significant increases in exchangeable sodium and extracellular fluid volume prior to the development of peripheral edema.

At this apparently new state of increased body sodium and extracellular fluid volume these patients appear to tolerate high dietary sodium intakes without developing an increase in their cardiac symptoms or in their body sodium and extracellular fluid volumes.

Dietary sodium restriction and diuretic therapy in these persons reduce the body sodium and extracellular fluid volume but not to normal levels.

Increases in pulmonary capillary pressure and decreases in renal plasma flow are the only consistent hemodynamic abnormalities noted in all these nonedematous patients with subclinical salt and water retention.

The findings suggest that a primary stimulus for expansion of extracellular fluid volume and body sodium to a new equilibrium level in congestive heart failure may involve distention of the pulmonary veins or the left atrium.

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Perinatal Vascular Changes in Coarctation of the Aorta with Distal Patent Ductus Arteriosus

By RICHARD L. NAEYE, M.D.

PULMONARY vascular changes often help to explain the circulatory abnormalities that develop in certain persons with congenital cardiac anomalies. Although such vascular changes have been described in some persons with coarctation of the aorta and distal patent ductus arteriosus,[1-5] the cause of the pulmonary hypertension in other cases has remained obscure.[1, 6] None of the reported studies of this type of coarctation has included quantitative comparisons of the two major circulatory beds. Such a study should provide useful information about the genesis of the high pulmonary vascular resistance in these cases.

Circulatory abnormalities in this disorder may alter the development of the vascular beds both before and after birth. Before birth, pressures in both sides of the heart may be elevated, as evidenced by the biventricular cardiac hypertrophy found in newborn infants with these anomalies.[1, 7, 8] After birth, since the ductus arteriosus remains patent, the lesser circulation and most of the greater circulation are subjected to a common pressure through a common ejectile force.[3] Under these circumstances, at least part of the pulmonary vascular resistance and pulmonary arterial muscle mass developed during fetal life may be retained.[1, 3, 4] The current report offers information regarding an abnormal development of the pulmonary vascular bed before birth in such cases. In addition, neonatal changes in both the greater and lesser circulatory beds are quantitated.

Subjects and Methods

Eighteen infants were examined who had coarctation of the aorta proximal to a widely patent ductus arteriosus. Two were stillborn, one at 28 weeks of gestation and the other at term. The remainder varied in postnatal age from several hours to 16 weeks. In all cases, the descending aorta was supplied almost entirely with pulmonary arterial blood, the coarctation being severe. In none of the cases were enlarged collateral vessels described that might have bypassed the coarctation. The heart was enlarged in all instances, usually being two to three times the normal weight. This hypertrophy usually involved the two ventricles about equally. Dilatation was commonly noted in both chambers of the right heart. No cases were included that had anomalies in addition to the coarctation and patent ductus.

Survival was so short in most of the group that clinical observations were scanty. Most were cyanotic at or soon after birth. In some of the infants this was continuous and in others episodic. In all but two of the cases, this cyanosis was thought to be generalized and not confined to the lower portion of the body. Cardiac systolic murmurs were detected in 11 of the infants. Feeding difficulties were common and those who survived for a time usually had a poor gain in weight. Most had evidence of congestive cardiac failure at autopsy with edema of the dependent soft tissues and enlarged, congested livers.

A special study was made of small arteries and arterioles because they presumably make a major contribution to vascular resistance. Previously described methods were used to measure arterial changes in both circulations.[9] In each case, multiple blocks of pulmonary tissue, selected at random, were sectioned at 6 μ and stained with Verhoeff's and Van Gieson's stains. Similar sections were prepared from one or more blocks of pancreas in 10 of the cases. With the aid of a camera lucida and a planimeter, the relative cross-sectional areas of lumen, intima, and media of muscular arteries and arterioles were determined. In each vessel, the internal elastic membrane was arbitrarily included as part of the intima. Sections from cases under study and sections from controls were thoroughly mixed and examined in a random manner to avoid bias.

Results

Initially, the mean area of intima combined with internal elastic membrane for small ar-

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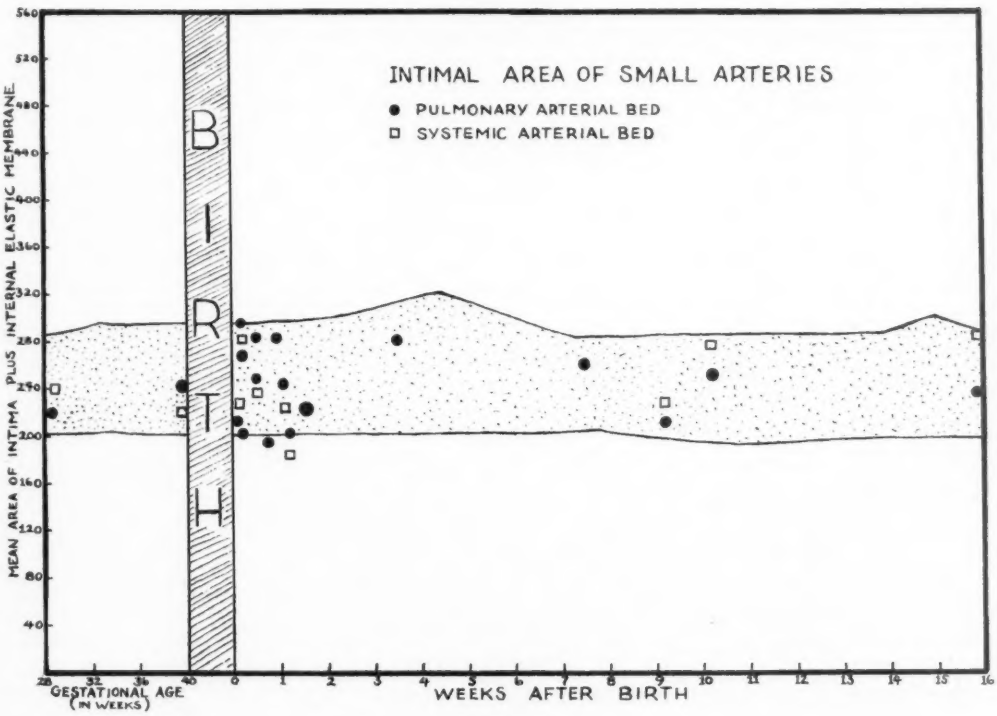

Figure 1

The mean areas of intima combined with internal elastic membrane for small arteries from patients with severe coarctation of the aorta and a distal patent ductus arteriosus. The areas in which normal values[9] are found are lightly shaded.

teries in each case was charted against stage of development (fig. 1). The values proved to be relatively similar and constant throughout the period of study for the two circulatory beds. Values for patients with coarctation and patent ductus arteriosus were also similar to those for normal controls. Comparable but larger values were recorded for medium-sized arteries. Therefore, the relative area of intima combined with internal elastic membrane was selected as a convenient reference baseline to which the arterial medial mass could be compared. As in the previous study,[9] a numerical expression:

$$\frac{\text{area arterial or arteriolar media}}{\text{area intima + internal elastic membrane}}$$

was adopted as a relative measure of arterial muscle mass. In each case, this value was determined for 15 to 30 arterioles and small arteries between 5 and 30 μ luminal diameter in each of the two circulatory beds. Similar determinations were made on arteries with luminal diameters between 30 and 50 μ.

In patients with coarctation of the aorta and distal patent ductus, systemic arteries and arterioles were found to be normal. Examination of the ratio

$$\frac{\text{area media}}{\text{area intima + internal elastic membrane}}$$

showed that the medial muscle of these vessels was normal in area (figs. 2 and 3). In contrast, the ratio for pulmonary arteries and arterioles was increased, both before and after birth (figs. 2 and 3). In the two stillborn infants, the relative pulmonary arterial muscle

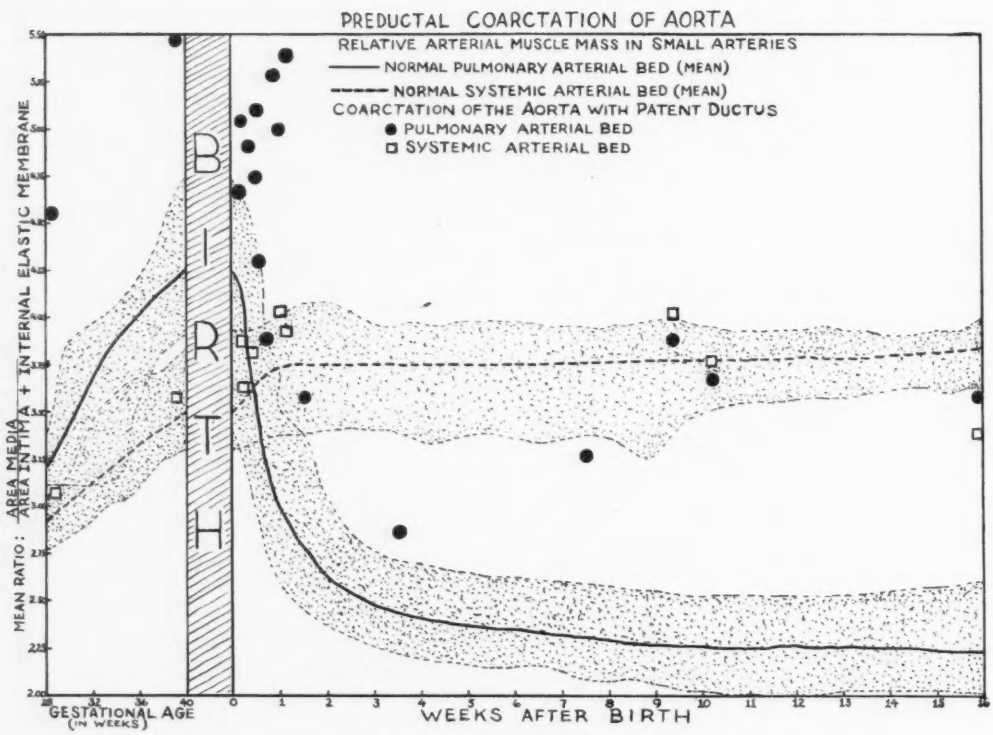
PREDUCTAL COARCTATION OF AORTA
RELATIVE ARTERIAL MUSCLE MASS IN SMALL ARTERIES
NORMAL PULMONARY ARTERIAL BED (MEAN)
NORMAL SYSTEMIC ARTERIAL BED (MEAN)
COARCTATION OF THE AORTA WITH PATENT DUCTUS
PULMONARY ARTERIAL BED
SYSTEMIC ARTERIAL BED
MEAN RATIO: AREA MEDIA / AREA INTIMA + INTERNAL ELASTIC MEMBRANE
BIRTH
GESTATIONAL AGE (IN WEEKS)
WEEKS AFTER BIRTH

Figure 2

A ratio reflecting arterial muscle for small arteries from patients with coarctation of the aorta and distal patent ductus arteriosus. The areas in which normal values[9] are found are lightly shaded.

mass was about 30 per cent greater than that found in control cases. There was greater variation in those who survived birth by less than a week, but the mean increase for all was approximately 25 per cent. In all instances, pulmonary arterial muscle mass was relatively greater than systemic arterial muscle mass during this period. Pulmonary arterial muscle mass remained far above normal levels in those who survived for a longer period (figs. 4 and 5). In at least two cases, however, it was below that found in the systemic arterial bed. In all cases, these changes were found in all of the arteries and arterioles studied, irrespective of size (figs. 2 and 3). Intimal or elastic membrane abnormalities were absent and the pulmonary veins and bronchial vessels were structurally normal.

Discussion

The study suggests that hemodynamic abnormalities exist in the right ventricle and pulmonary circulation during fetal life in infants having severe coarctation of the aorta with distal patent ductus arteriosus. Such infants have an increased pulmonary arterial muscle mass and hypertrophy of the right ventricular wall. These are probably related to right ventricular and pulmonary arterial hypertension. An enlarged right ventricular cavity in many of these infants suggests an increased capacity of that chamber and possibly an increased right ventricular output. It is possible that these changes arise independent of the coarctation but it is more likely that they are related. They are probably the consequence of functional and structural al-

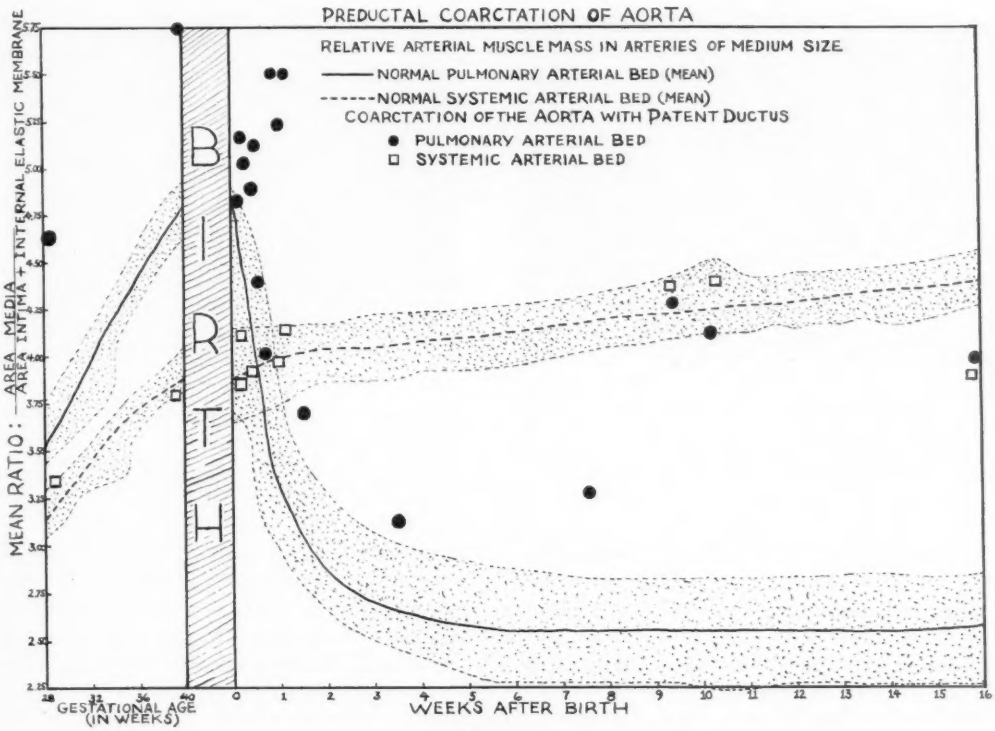
PREDUCTAL COARCTATION OF AORTA
RELATIVE ARTERIAL MUSCLE MASS IN ARTERIES OF MEDIUM SIZE
NORMAL PULMONARY ARTERIAL BED (MEAN)
NORMAL SYSTEMIC ARTERIAL BED (MEAN)
COARCTATION OF THE AORTA WITH PATENT DUCTUS
PULMONARY ARTERIAL BED
SYSTEMIC ARTERIAL BED
MEAN RATIO: AREA MEDIA / AREA INTIMA + INTERNAL ELASTIC MEMBRANE
BIRTH
GESTATIONAL AGE (IN WEEKS)
WEEKS AFTER BIRTH

Figure 3

A ratio reflecting arterial muscle for medium-sized arteries from patients with coarctation of the aorta and distal patent ductus arteriosus. Normal values are found within the shaded areas.[9]

terations in the left ventricle. It is also possible that the pulmonary arterial changes influence postnatal survival of these infants.

Left ventricular hypertrophy was noted in our stillborn infants and has been reported by others.[1, 7] The coarctation, developing during fetal life, presumably leads to rises in left ventricular pressure and an abnormal work hypertrophy of this chamber's wall. It is postulated that this hypertrophy reduces the distensibility of the left ventricle, leading to a rise in the diastolic filling pressure of that chamber. A portion of the blood in the common atrial pool that normally passes to the left ventricle during fetal life is presumably diverted to the right ventricle. The consequent increase in right ventricular output might well require an increased capacity and pressure in that chamber. This could lead to the observed changes in the right ventricle and to the increased pulmonary arterial muscle mass. Similar reasoning can be applied to cases in which the fetal output of the right ventricle is increased as a result of premature closure of the foramen ovale. The right ventricle is hypertrophied and dilated in such infants at birth and they have an increase in pulmonary arterial muscle mass.[10]

The validity of this hypothesis depends on a demonstration that the prenatal left ventricular hypertrophy may lead to a reduction in the normally large right-to-left shunt through the foramen ovale. Edwards[5] has illustrated a related mechanism in certain adults with interatrial septal defect. When the right ventricular wall becomes thicker

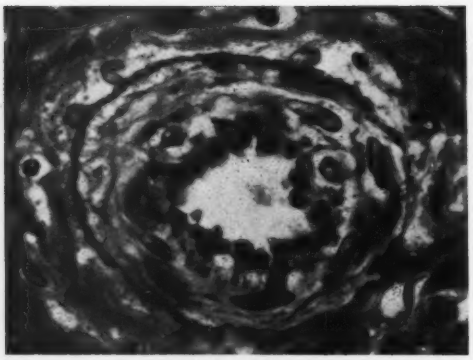

Figure 4

Pulmonary muscular artery from a 10-week-old infant. The medial muscle mass is conspicuous. The vessel is more contracted than are most pulmonary arteries in infants with preductal coarctation of the aorta. Verhoeff's and Van Gieson's stains.

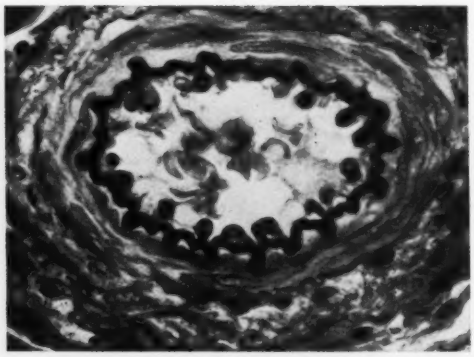

Figure 5

Pancreatic muscular artery from the case shown in figure 4. The arterial muscle mass is somewhat less than that seen in a comparable pulmonary artery (fig. 4). Verhoeff's and Van Gieson's stains.

than the left in such individuals, diastolic filling pressures on the right presumably exceed those on the left, and a part of the blood in the right atrial portion of the common atrial pool is diverted to the left ventricle. Thus, it is possible that ventricular wall thickness and distensibility are sometimes related. From another viewpoint, the increased ventricular diastolic filling pressures that alter the interatrial shunts may be related to early ventricular failure in both Edwards' cases and our own.

In our infants with coarctation of the aorta proximal to a patent ductus, the prenatal pulmonary vascular changes were continued after birth. Smooth muscle about the pulmonary arterial bed did not rapidly decrease as it does in normal infants. During the early weeks it was maintained at the birth level in some cases and at levels intermediate between the birth and normal levels in other cases. This continued abnormal development can be attributed to at least two factors. First, the pulmonary and lower systemic circulations were subjected to a common systolic pressure through the patent ductus arteriosus. Persistence of the fetal pulmonary arterial muscle mass has been attributed to this common pressure.[1, 5] Secondly, hypoxemia may have played a role. Cyanosis was prominent in most of our cases. Although the full mechanism is unknown, hypoxemia can induce an increase in pulmonary vascular resistance in normal newborn infants[11] and might also do so in infants with preductal coarctation of the aorta. It is known that hypoxemia can induce directly or indirectly the development of an increased muscle mass about the pulmonary arterial bed.[12]

What relationship does the hypertrophied pulmonary arterial muscle mass have to pulmonary vascular resistance in these cases? Direct prenatal data are not available but may be at least partially inferred from information available during the early postnatal period. Neonatal cardiac catheterization in several cases has shown a right-to-left shunt across the ductus arteriosus with high pulmonary arterial pressures.[13, 14] Such findings suggest a greatly elevated pulmonary vascular resistance. Additional evidence for a high pulmonary vascular resistance was the generalized cyanosis noted in most of our cases. Cyanosis in the lower part of the body in such infants is easily explained by the fact that it was directly perfused by unsaturated blood from the right heart. Cyanosis in the upper part of the body, however, was most likely related to a high extraction of oxygen at the tissue level. Such stagnation cyanosis would imply an in-

adequate left ventricular output, possibly due to an abnormally elevated pulmonary vascular resistance, which reduced pulmonary venous return. The very maintenance of an appreciable lower systemic flow in such cases is evidence that pulmonary vascular resistance is abnormally high. If the pulmonary resistance were to fall to normal levels, the consequent runoff into the lesser circulation would reduce systemic flow below the coarctation to a point incompatible with life.[3]

The evidence that the hypertrophied arterial muscle mass is responsible for the elevated pulmonary vascular resistance is indirect. The appearance of the small arteries and arterioles with their thick muscular layers suggests that they are capable of significant degrees of vascular constriction. Most important is the fact that the hypertrophied muscle is the only anatomic change in the lesser circulation that might easily explain the abnormal resistance. No microscopic abnormalities were noted in the pulmonary capillaries and veins of our infants and the submicroscopic structures of the pulmonary capillary bed in such cases is also presumably normal.[15]

An increased tone in such hypertrophied muscle can be demonstrated by two different methods. The change from breathing air to 99 per cent oxygen in such infants is accompanied by a fall in pulmonary arterial pressures.[13] In addition, acetylcholine injected into the pulmonary artery causes a fall in pressure and an increase in pulmonary flow in patients with related anomalies.[16] A reduced pulmonary vascular resistance after operative correction of the anomalies[17, 18] could again be most easily explained by a decrease in pulmonary arterial tone and muscle mass.

The short postnatal survival of infants with these anomalies requires further comment. About 90 per cent die within a year of birth, most within the first weeks or months.[19, 20] In addition to the elevated pulmonary vascular resistance several other factors may contribute to the progressive cardiac failure that commonly develops. With the presumed rise in pulmonary blood flow after birth, the work of the right heart is probably greatly increased in maintaining flow through the lower systemic bed. The poor oxygen supply at the tissue level could be expected to increase the demand for cardiac output with a consequent relative reduction in myocardial reserve. The work of the left heart may well be increased by the increased pulmonary venous return. In addition, left heart reserve is undoubtedly also reduced by continued outflow obstruction at the point of coarctation. The failure after birth to develop collateral vessels that might bypass the coarctation is presumably an important factor in the short survival of these infants.[21] Despite these problems, all the hemodynamic abnormalities are apparently reversible following surgical correction.[20]

Summary

Infants with severe coarctation of the aorta and patent ductus arteriosus develop an increased pulmonary arterial muscle mass and hypertrophy of the right ventricle during fetal life. Much of this arterial muscle mass is retained after birth. The development of the systemic arterial bed is normal during both periods.

Acknowledgment

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There are, in truth, no specialties in medicine, since to know fully many of the most important diseases a man must be familiar with their manifestations in many organs.—SIR WILLIAM OSLER. *Aphorisms From His Bedside Teachings and Writings.* Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 54.

Myocardial Infarction and Atrial Arrhythmias

By THOMAS N. JAMES, M.D.

ATRIAL ARRHYTHMIAS occur in about 10 per cent of acute myocardial infarctions and the commonest of these arrhythmias is atrial fibrillation.[1] When atrial fibrillation is sustained after beginning during myocardial infarction, it has been reported to be associated with an 89 per cent mortality.[2] Although there have been a number of studies on the clinical aspects of the association of such rhythm disturbances with myocardial infarction,[3-9] little is known regarding their pathogenesis.

This is a report of findings from 11 selected cases of patients with myocardial infarction who developed atrial arrhythmias. All were necropsied. Each heart was carefully dissected to determine the manner of blood supply to the atria as well as the ventricles, and special attention was given to the blood supply to the sinus node and AV (atrioventricular) node.[10, 11] Note was made whether occlusions in the main coronary artery were proximal or distal to the origin of the nodal arteries. For histologic study the sinus and AV nodes were cut serially at 2 mm. intervals in all 11 cases.

Because atrial fibrillation both clinically and experimentally is so closely related to other atrial arrhythmias (atrial flutter, atrial tachycardia, etc.), the terms "atrial fibrillation" and "atrial arrhythmias" in general are used interchangeably.

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Case Reports

Case 1

R.C., a 53-year-old man, died of subacute bacterial endocarditis with rupture of the aortic valve, and lamellar myocardial infarction of both ventricles. His final illness was associated with multiple atrial arrhythmias (fig. 1). At necropsy there was marked compromise of the lumen of the left circumflex artery by old sclerosis, and this artery crossed the crux to supply the AV node; in addition there was a recent occlusion of the small right coronary artery proximal to the origin of the sinus node artery (fig. 2). Ecchymoses were present in the epicardium of the sulcus terminalis over the sinus node, and these corresponded to infarction of the node seen microscopically (figs. 3 and 4). No pathology was found in the AV node.

Case 2

M.K., a 68-year-old woman, died during an acute anterolateral myocardial infarction with atrial fibrillation. At necropsy most of the left ventricle was infarcted and a fresh thrombus occluded the main left coronary artery; the sinus node artery arose from the left circumflex branch. There was an old occlusion of the right coronary artery just beyond the margo acutus and proximal to the AV node, which it supplied. There was infarction of the sinus node (fig. 5), but no pathology was found in the AV node.

Case 3

J.D.H., a 78-year-old man, died of an acute myocardial infarction of the left ventricular free wall and septum. His final illness included the onset of atrial fibrillation. At necropsy there was a recent occlusion of the main left coronary artery, plus an old occlusion of the right coronary artery proximal to the origins of the arteries supplying both the sinus node and AV node. In the sulcus terminalis there were gross epicardial hemorrhages over the sinus node (fig. 6), which corresponded to a hemorrhagic infarction seen histologically (fig. 7). There was no infarction in the AV node.

Case 4

H.L., a 72-year-old man, died of an acute posterior myocardial infarction. Initially his electrocardiogram showed incomplete AV block but later

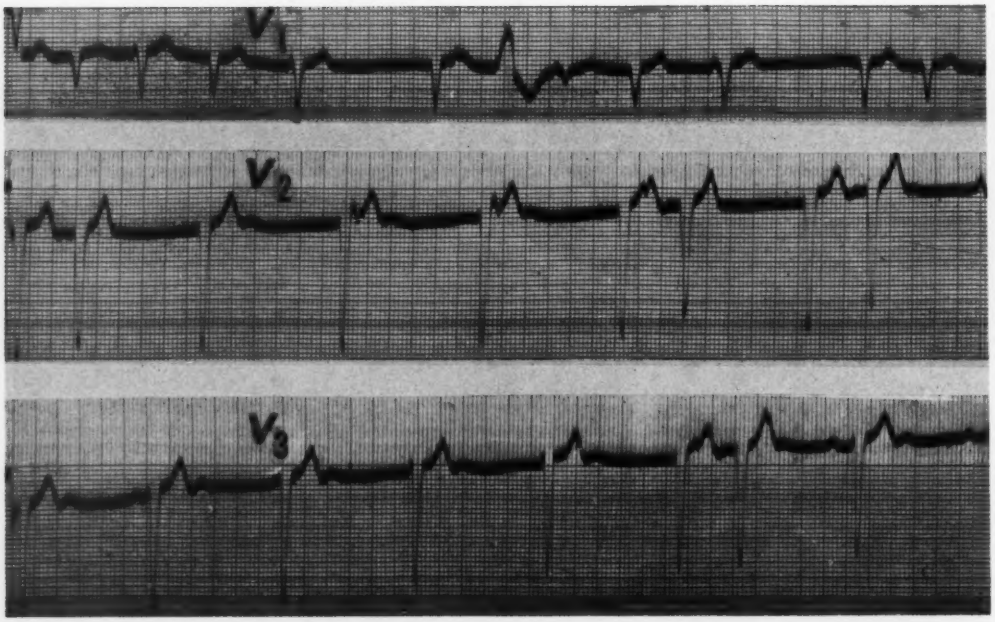

Figure 1

Electrocardiogram of case 1, showing intermittent sinus node activity.

he developed atrial fibrillation (fig. 8). At necropsy there were two recent occlusions, one in the right coronary artery at the margo acutus and the other at the origin of the left anterior descending artery, compromising the lumen of the main left coronary artery also. The sinus node artery arose from the left circumflex branch, adjacent to the main left coronary artery, and was partially involved by the recent occlusion. The right coronary artery crossed the crux of the heart and supplied the AV node. Histologically, old and new infarction involved most of the sinus node exit junctions (fig. 9); in the AV node there was lesser damage.

Case 5

T.S., a 64-year-old man, died of congestive failure due to intractable atrial fibrillation with rapid ventricular response. At necropsy there was old occlusion of the left anterior descending, the left circumflex, and right coronary arteries. The right coronary occlusion was proximal to the origin of both nodal arteries (fig. 10). Except for some small new foci the ventricular infarction in most of the left ventricle was old. In the epicardium of the sulcus terminalis there were ecchymoses over the sinus node (fig. 11), corresponding to infarction present microscopically (figs. 12 and 13). No pathology was found in the AV node.

Case 6

L.V., a 61-year-old man, died of an acute posterolateral myocardial infarction during which he developed atrial fibrillation. At necropsy there was an old occlusion of the right coronary artery at the margo acutus, with that artery supplying an unusually large area of the posterior and lateral left ventricle, as well as the AV node. There was also a recent occlusion of the smaller main left coronary artery proximal to the origin of the sinus node artery, which arose from the even smaller left circumflex artery. There was infarction at the exit junctions of the sinus node, and marked sclerosis of the AV node artery (fig. 14); no other pathology was found in the AV node.

Case 7

C.C.B., a 66-year-old man, died of posterior myocardial infarction during which he developed an atrial tachycardia of 176 per minute. At necropsy there was a recent occlusion of the right coronary artery proximal to the origin of the sinus node artery, the right coronary continuing to supply the posterior wall and AV node. Ecchymoses were present in the epicardium over the sinus node (fig. 15) and infarction was present in the sinus node. No pathology was found in the AV node.

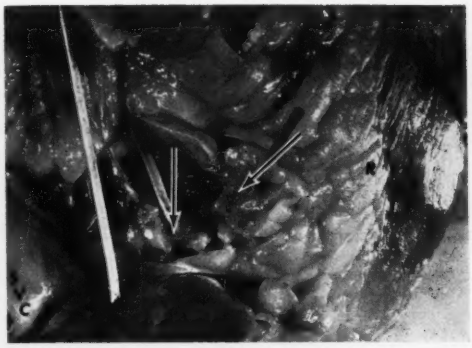

Figure 2

Photograph of the heart, case 1. Right arrow indicates the cut edge of a recent occlusion of the right coronary artery; left arrow indicates the sinus node artery, which arose distal to the occlusion. Ao, is the aorta; Ap, the right atrial appendage; SVC, the superior vena cava; and RV, the right ventricle.

Figure 3

A low-power photomicrograph of the sinus node, case 1. In this and subsequent photomicrographs N refers to the sinus node and A to the right atrium. There is hemorrhage and infarction at the junction of the node and atrium.

Case 8

V.H., a 62-year-old man, died of a large anterolateral myocardial infarction, during which he developed atrial fibrillation. At necropsy there was an old occlusion of the right coronary artery proximal to where it crossed the crux, supplying the AV node. The left circumflex artery was occluded by an old lesion at the origin of the sinus node artery, and the left anterior descending artery was occluded by a fresh thrombus 2 cm. from its origin. Infarction was found in both the sinus node and AV node.

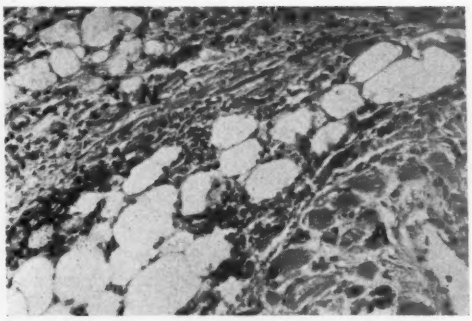

Figure 4

Higher power photomicrograph of the sinus node, case 1, showing hemorrhage and degeneration at the junction of the node and atrium.

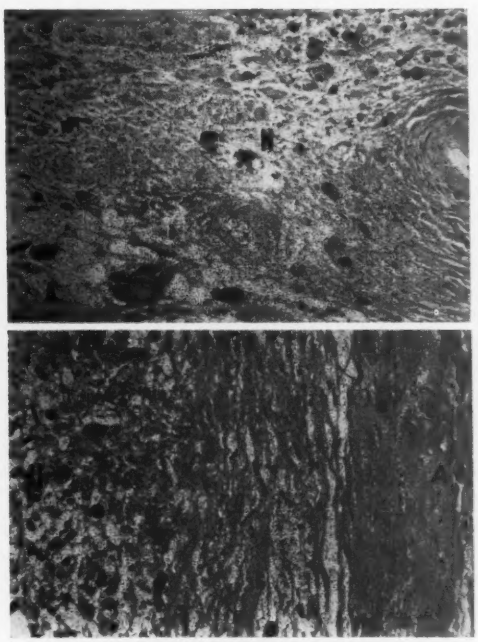

Figure 5

Two photomicrographs of the sinus node, case 2, showing congestion and hemorrhage at the junction of the node and atrium under low power (top) *and high power* (bottom).

Case 9

W.G., a 64-year-old man, died of acute posterior myocardial infarction. In his final illness he had a variety of atrial arrhythmias, including atrial fibrillation. At necropsy there was a recent occlusion of the left circumflex coronary artery near

Figure 6

Photograph of the sinoatrial junction of the heart of case 3. Arrow points to the ecchymoses in the sulcus terminalis directly overlying the sinus node; RA is right atrium.

the margo obtusus, with the circumflex artery continuing to the crux of the heart and posterior left ventricle, supplying the AV node. There was an old occlusion of the relatively small right coronary artery proximal to the origin of the sinus node artery. Gross ecchymoses were present in the epicardium of the sulcus terminalis over the sinus node; these corresponded to an infarction of the sinus node seen microscopically (fig. 16). No pathology was found in the AV node.

Case 10

W.S., a 48-year-old man, had a posterior myocardial infarction 1 year previously and then died during a lateral infarction. During both of these he had intermittent cessation of sinus node activity (fig. 17). At necropsy there was infarction of most of the left ventricle, with old occlusions of both the left anterior descending artery and the left circumflex artery. The latter vessel supplied the AV node and the entire left ventricle except the anteroseptal portion, the right coronary artery being diminutive. There was a fresh occlusion in the first centimeter of the left circumflex artery, the sinus node artery arising distal to this, at a point of old occlusion near the margo obtusus. Infarction was present in both the sinus node and AV node.

Case 11

T.L.D., a 66-year-old man, died of myocardial insufficiency during intractable atrial flutter and fibrillation with a rapid ventricular response; he also had hemachromatosis. At necropsy there was old occlusion of the left anterior descending artery and of the right coronary artery proximal to the origin of the sinus node artery; the right coronary continued to the crux of the heart to supply the posterior wall and AV node. Ventricular infarction was streaky and both old and new. There were edema and hemorrhage at the exit junctions of the sinus node. Degenerative changes were present in the AV node about iron deposits (fig. 18); despite careful searching, no iron could be demonstrated in the sinus node.

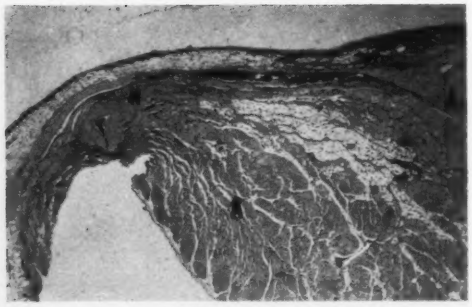

Figure 7

A low-power photomicrograph of the sinus node of case 3, showing hemorrhages in the epicardium and at the junctions of the node and atrium.

Comment on the Eleven Cases

In all 11 cases a coronary occlusion was present proximal to the origins of both the sinus node artery and AV node artery. In six of the hearts gross ecchymoses were found in the sulcus terminalis directly over the sinus node. Data relating the nodal histopathology to the arrhythmias are presented in table 1.

Microscopically, infarction of the sinus node was found in all 11 cases. Lesser changes were apparent in the AV node in five cases. These changes were acute and consisted primarily of hemorrhage and edema; however, collagen deposition and fatty infiltration were present in scattered foci of all the sinus nodes, suggesting that previous focal damage had occurred.

The sites of damage in the sinus node were characteristic in every case, occurring at the junctions of the node with the right atrium and sinus intercavarum. Hemorrhages at these locations involved Purkinje tracts leaving the node and may be presumed to be asso-

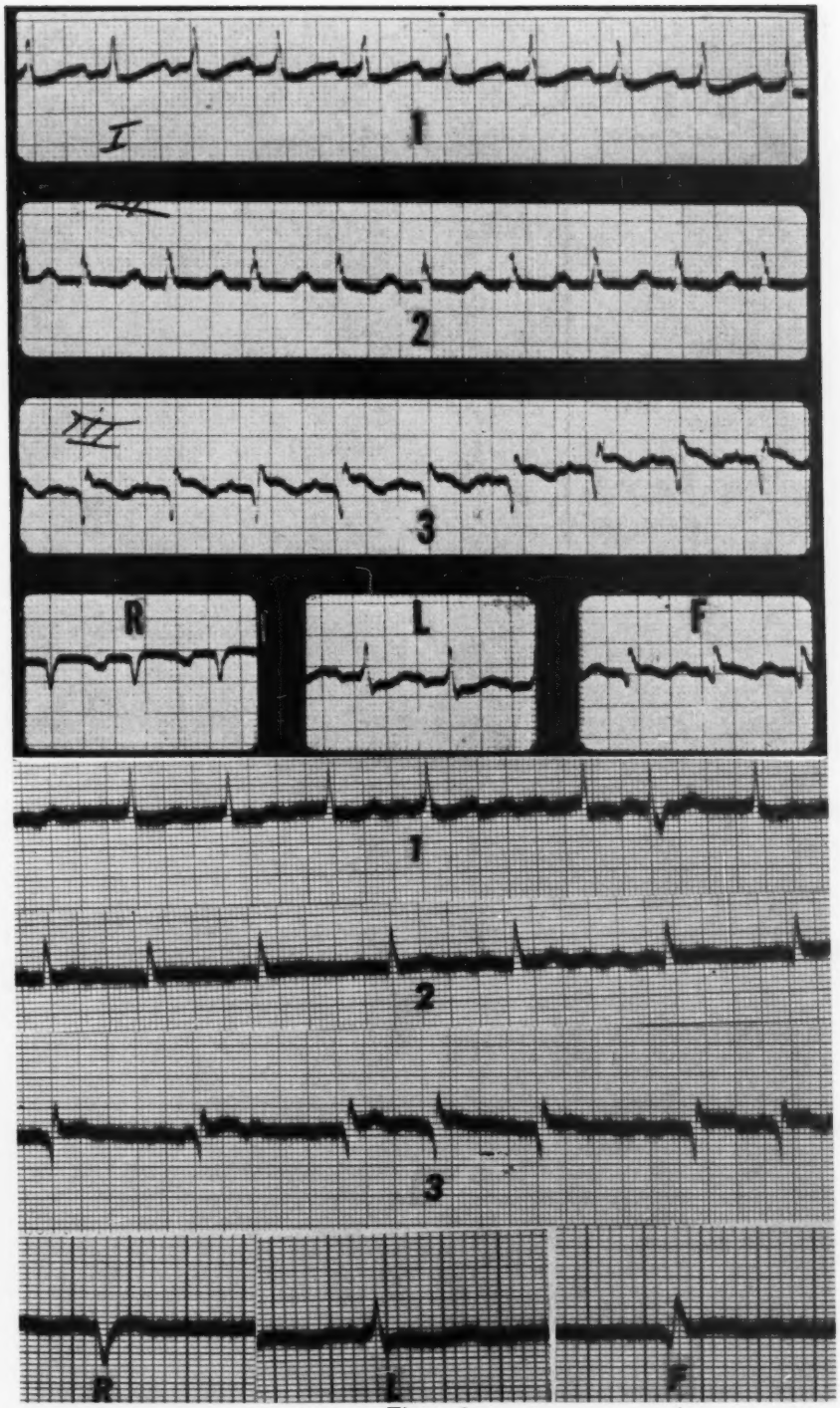

Figure 8

Two electrocardiograms from case 4 showing incomplete AV block (P-R time 0.26 second) at the onset of an acute posterior myocardial infarction (top), *and atrial fibrillation 2 days later* (bottom).

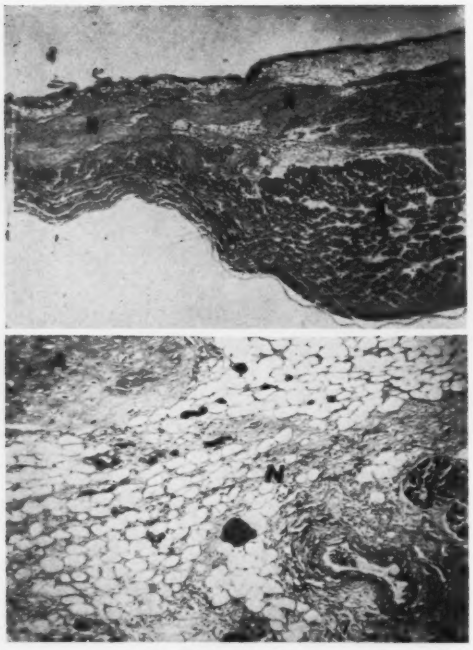

Figure 9

Low-power (top) *and high-power* (bottom) *photomicrographs of the sinus node, case 4, showing fibrosis, fatty replacement, and recent hemorrhage at the junction of the sinus node and atrium.*

ciated with impairment of normal transmission of the sinus impulse to the rest of the heart. Pathologic changes were less often seen in the central portion of the node or in the more distal atrial muscle, suggesting that the exit junctions of the node may be peculiarly vulnerable to acute hypoxia.

Histopathology of the AV node was less consistent and less striking. Presence of an occlusion in the main coronary artery proximal to the origin of the AV node artery in all 11 cases certainly suggests that those AV nodes must have been rendered hypoxic. The possible contribution of this AV nodal hypoxia to the pathogenesis of atrial arrhythmias is discussed later; however, at present this remains a speculative probability.

Discussion

Although it has long been thought that atrial arrhythmias in acute myocardial infarction probably represent concomitant

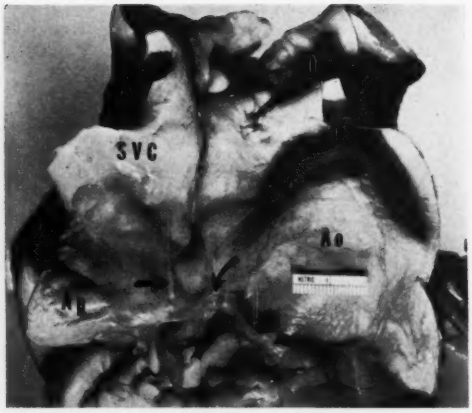

Figure 10

Photograph of the heart of case 5, demonstrating the sinus node artery (left arrow) arising from the right coronary artery (right arrow); in the knuckle of right coronary artery indicated by the curved arrow there was a complete occlusion. Ao, the aorta; Ap, the right atrial appendage; SVC, the superior vena cava. The sinus node artery courses into the sinus node at the junction of the atrial appendage and vena cava.

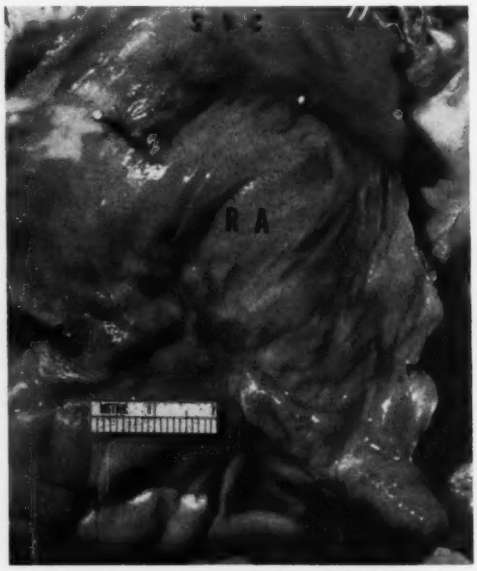

Figure 11

Another view of the heart in figure 10 (case 5), demonstrating the ecchymoses in the sulcus terminalis over the sinus node, being the area between the two pin heads. SVC, the superior vena cava; and RA, the right atrium.

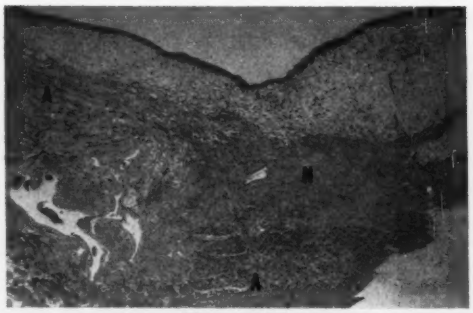

Figure 12A

Low-power photomicrograph of the sinus node from case 5. Hemorrhagic infarction is present between the body of the node and the atrium.

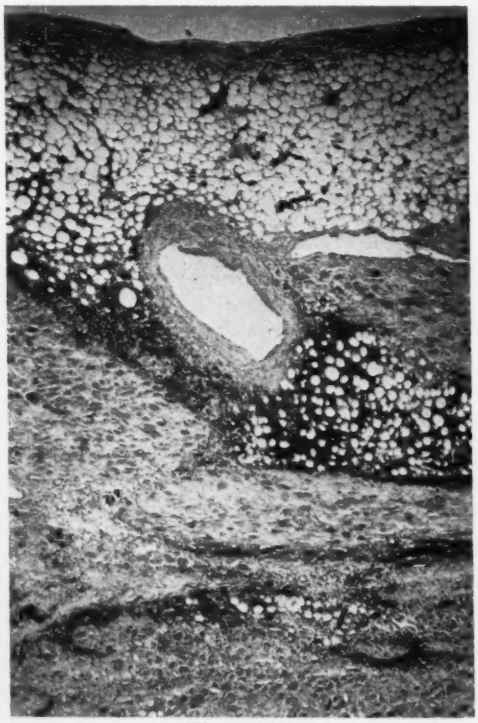

Figure 12B

Low-power photomicrograph through the tail of the node, 10 mm. from figure 12A. Hemorrhage and old fibrosis have virtually replaced the node.

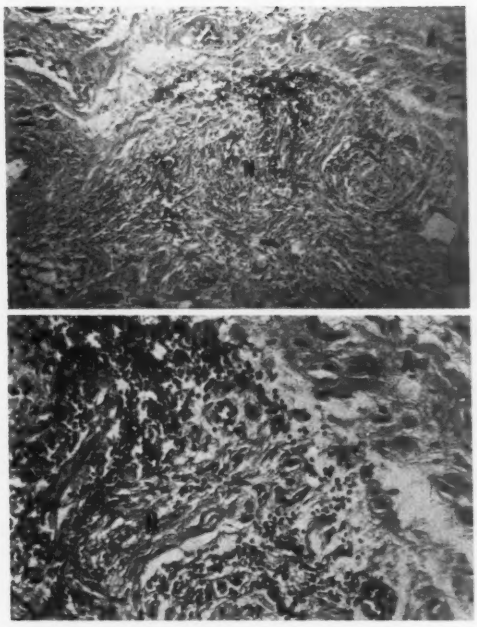

Figure 13

Medium-power (top) *and high-power* (bottom) *photomicrographs of the hemorrhagic infarction at the junction of the node and atrium (case 5).*

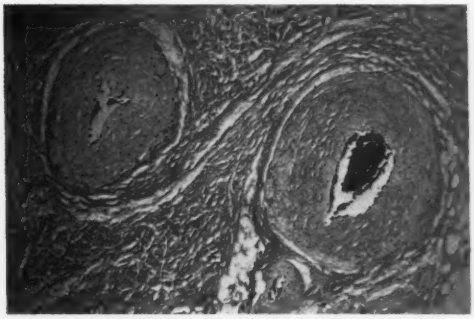

Figure 14

Photomicrograph of the two branches of the AV node artery, both sclerosed for more than 75 per cent of their lumina and surrounded by morphologically normal AV node (case 6).

atrial damage, evidence to support this clinical impression has been meager. A notable exception was the demonstration by Cushing et al.[12] that the commonest clinically recognizable manifestation of atrial infarction was the presence of an atrial arrhythmia, but they did not specifically relate these observations to the pacemaker of the heart. Atrial infarction in experimental animals is not, however, associated with regular production of atrial

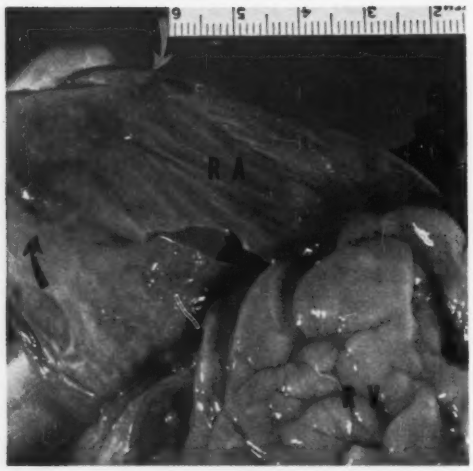

Figure 15

Photograph of the heart from case 7, showing the ecchymoses in the sulcus terminalis over the sinus node, indicated between the two arrows. RA, the right atrium; RV, the right ventricle.

arrhythmias,[13, 14] and ligation of the primary blood supply to the sinus node of the dog only rarely disturbs the sinus rhythm.[15] It must be concluded that atrial arrhythmias occurring during acute myocardial infarction have a more complex pathogenesis.

There are few studies on the pathology of the sinus node, exceptions being the recent reports of Lev[16, 17] and Hudson.[18] Lev observed that increasing fibrosis in the sinus node is a normal consequence of aging, making evaluation of old focal lesions there difficult. Hudson has noted that various pathologic changes in the sinus node are by no means uncommon.

Based on a study of the 11 cases reported here, and a review of the published observations on this subject, the following factors may be considered as influencing the onset of atrial fibrillation (or other atrial arrhythmias) during acute myocardial infarction:

1. Depressed sinus node "dominance."
2. Impaired sinus impulse transmission.
3. Vagal and vagomimetic reflexes.
4. AV node injury.
5. Extranodal atrial injury.

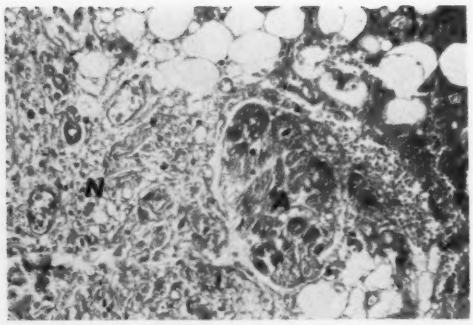

Figure 16

Photomicrograph of the sinus node of case 9. There is hemorrhage at the junction of the node and atrium, with degeneration of the node.

6. Atrial distention.
7. Hypercalcemia.
8. Increased circulating catecholamines.
9. Iatrogenic factors.

Usually more than one of these factors is present in any given case, but each is discussed separately.

Depressed Sinus Node "Dominance"

Since the cardiac pacemaker is naturally so located that its regular stimulation of the heart is distributed with maximal efficiency, any condition producing sustained replacement of sinus rhythm by some other rhythm must either destroy or weaken the sinus impulse, block this impulse, or be of such strong potential itself as to supersede this impulse. Experimental application of aconitine to canine atria is an example of the latter, but it is significant that atrial fibrillation so induced is self limiting, and aconitine must be reapplied if the arrhythmia is to be sustained; as the extranodal impulse weakens, the undamaged sinus node resumes dominance.

Whether transmission of the sinus impulse from the node to the atria can be suppressed without damage to the sinus node and atrium is problematical. That the impulse can be blocked in its passage from the atria to the ventricles without damaging the AV node is well substantiated both experimentally and clinically, and the role of such block is discussed later.

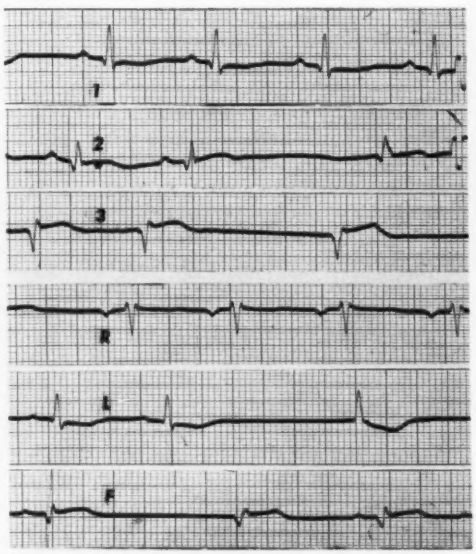

Figure 17

Electrocardiogram (case 10) showing intermittent cessation of sinus node activity during an acute posterior myocardial infarction.

The present observations suggest that ischemia or injury of the human sinus node influences the onset of atrial fibrillation in myocardial infarction. That this alone is inadequate to produce such arrhythmia was long ago suggested by the persistence of regular rhythm following destruction of the region of the sinus node,[19, 20] and further suggested by the persistence of sinus rhythm following ligation of the sinus node artery of the dog.[15] It must nevertheless be presumed that ischemia or injury of the sinus node, by weakening normal sinus node dominance of the heart, is an important factor in this problem, and particularly a factor in prolongation or sustaining of such arrhythmias.

Another important factor depressing sinus node "dominance" is vagotonia. That some vagotonia occurs in most acute myocardial infarctions can little be doubted. It has even been stated that increased vagal tone is the universal mechanism of sudden death in myocardial infarction.[21] The effect on the sinus node of increasing vagal tone (especially the

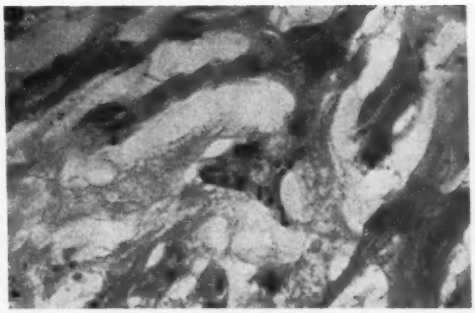

Figure 18

High-power photomicrograph from the AV node of case 11, demonstrating iron deposits and degeneration of the nodal fibers in this patient with hemachromatosis.

right vagus) is well known[22, 23] and consists of increasing bradycardia to ultimate cessation of all sinus node activity. When this occurs in a patient with other factors favoring the onset of atrial fibrillation, it must be presumed to contribute to the onset of the arrhythmia. In addition there are other effects of vagal stimulation that favor the onset of fibrillation, such as increasing the normal disparity of repolarization speed in atrial fibers.[24]

Sinus arrest observed during acute myocardial infarction may be the result of either vagotonia or sinus node ischemia or both, and the clinical differentiation of the two factors may be difficult. Atropine counteracts vagotonia, but its effect on sinus bradycardia or sinus arrest due to ischemic weakening of sinus impulse formation is unknown. In man, vagotonia encountered clinically is unlikely to be unilateral, and bilateral vagotonia should result not only in sinus bradycardia but also prolongation of AV conduction time; in myocardial infarction, however, not only is there likely to be bilateral vagotonia, but both sinus and AV nodes may be rendered ischemic at the same time by a coronary occlusion proximal to both their nutrient arteries. In every case in this study the main coronary arteries were occluded proximal to the origin of the blood supply of both nodes.

Table 1

Summary of the Arrhythmias and Nodal Pathology in 11 Cases of Myocardial Infarction

Case	Sinus node	AV node	Atrial arrhythmias
1	Infarcted	No pathology found	Multiple atrial arrhythmias
2	Infarcted	No pathology found	Atrial fibrillation
3	Infarcted	No pathology found	Atrial fibrillation
4	Infarcted	Infarcted	Incomplete AV block, then atrial fibrillation
5	Infarcted	No pathology found	Atrial fibrillation
6	Infarcted	Sclerotic AV node artery	Atrial fibrillation
7	Infarcted	No pathology found	Atrial tachycardia (176/minute)
8	Infarcted	Infarcted	Atrial fibrillation
9	Infarcted	No pathology found	Multiple atrial arrhythmias
10	Infarcted	Infarcted	Intermittent sinus arrest
11	Infarcted	Degeneration	Atrial flutter then fibrillation

Impaired Sinus Impulse Transmission

In all 11 of the cases, infarction occurred at the junctions of the sinus node with the right atrium and sinus intercavarum, regions through which the normal sinus impulse must pass to the heart. Although hemorrhages at these points were impressive, in none of the hearts were *all* the junctions damaged, so that potential points of exit still existed.

Since potential points of exit still were present, and since in experimental animals virtually all the connections to the sinus node can be severed without the occurrence of atrial fibrillation,[20] it must be concluded that impaired sinus impulse transmission, like suppressed sinus node "dominance," may be a contributing factor to the onset of atrial fibrillation during myocardial infarction, but that it is rarely capable of producing this effect by itself.

Other factors that may impair sinus impulse transmission during acute myocardial infarction are atrial distention and cellular anoxia. In the presence of congestive heart failure atrial pressure rises and the atrium distends as the ventricle fails to empty; in addition to the reflex effects of atrial distention,[25] the stretching of the atrial fibers lengthens the distance the normal impulse must travel, as well as probably further increasing the normal disparity of atrial fiber repolarization. Hypoxia of the atrial fibers during acute myocardial infarction also contributes to atrial dilatation, impaired atrial conduction, and increase in normal disparity of atrial fiber repolarization.

Vagal and Vagomimetic Reflexes

The effects of these very important reflexes that contribute to the onset of atrial fibrillation during acute myocardial infarction are discussed in detail under the other headings. Both the origin and specific pathways of these reflexes in acute myocardial infarction are poorly understood. For possible mechanisms and routes, considering the pathophysiology of acute myocardial infarction, one may consult the comprehensive reviews of cardiovascular reflexes.[25-29]

AV Node Injury

The AV node is an efficient alternate cardiac pacemaker. Persistence of an efficient regular cardiac rhythm in experiments in which the sinus node is destroyed is most likely due to assumption of pacemaking by the AV node or juxtanodal centers. It seems most reasonable, therefore, to believe that main coronary artery occlusions that compromise the blood supply to both the sinus node and AV node are more likely to evoke a disorganized rhythm than occlusions that compromise the blood supply of only the sinus node. This proved to be the case in the present study.

Since the right coronary artery supplies the AV node in about 90 per cent of human hearts, and the sinus node in about 55 per cent,[10, 11, 30] it is occlusion proximal to the

origin of the sinus node artery in the right coronary artery that is most likely to be associated with atrial fibrillation.

Klainer and Altschule[31, 32] observed that patients who developed atrial arrhythmias during myocardial infarction often had prolongation of the P-R interval in their electrocardiograms prior to the onset of the arrhythmia, and further that this AV block could be reduced by the administration of atropine. Although this is strong evidence that a vagomimetic influence on the AV node was present in their cases, the possibility that the AV block was due to ischemia or damage to the AV node rather than to vagotonia was not discussed, and the histology of the node was not reported.

Injury to the AV node may impair AV conduction sufficiently to reduce cardiac output and coronary flow. The importance of reduced coronary flow in the pathogenesis of arrhythmias during acute myocardial infarction has recently been stressed by Corday and others.[33, 34]

Extranodal Atrial Injury

Cushing et al.[12] emphasized the clinical importance of atrial arrhythmias in atrial infarction. Although damage to the sinus node is probably the most important atrial injury, damage to the "working" muscle of the atria may also contribute to the onset of atrial arrhythmias during acute myocardial infarction. For example, irritable atrial muscle at the periphery of such injury may establish a competing ectopic pacemaker, eager to take over if the sinus node should fail. Such a pacemaker may remain regular, but would more likely deteriorate to fibrillation, especially under the influence of other factors.

Additionally extranodal atrial injury may impair normal sinus impulse transmission, a factor already discussed, and increase further the normal disparity of repolarization speed in atrial fibers.[24] A weakened area of atrial muscle may also contribute to atrial dilatation from any other cause.

Since the sinus node artery is the largest and most constant atrial artery in man,[30] one might expect an occlusion proximal to its origin to produce a large atrial infarct. This did not prove to be the case in the 11 cases studied, only four of the 11 having a grossly recognizable atrial infarct, and the largest of these was less than 1 cm.^{2} in size; all four were in the right atrium. Thus extranodal atrial injury does not seem to be a regular accompaniment of sinus node infarction, but is an associated factor contributing to the onset of atrial arrhythmias in less than half of the cases.

Atrial Distention

Although listed separately as a contributing factor to atrial arrhythmias during myocardial infarction, which it is, atrial distention's specific effects and causes have been discussed under other headings.

Hypercalcemia and Increased Circulating Catecholamines

Both these factors influence the onset of atrial fibrillation during acute myocardial infarction through their effect on repolarization speed and are discussed together, although their pathogenesis differs. They further increase the normal disparity of repolarization speed in atrial fibers,[22-24] thus favoring both onset and perpetuation of fibrillation. They may also enhance any potential ectopic pacemaker.

Kleitman has shown that in man hypercalcemia normally occurs within a very short time after assuming the supine position.[25] Furthermore, this increase in circulating calcium was in the ionizable, or biologically active, form. Although it is well known that prolonged inactivity, as in poliomyelitis, is associated with increased calcium mobilization,[36] it is unlikely that these observations are applicable to patients placed at bed rest because of acute myocardial infarction. Kleitman's observations, however, are certainly pertinent and need to be studied further.

An increase in circulating catecholamines during acute myocardial infarction has been observed.[37] When of sufficient quantity these would not only have a chronotropic effect, but might raise the arterial blood pressure and

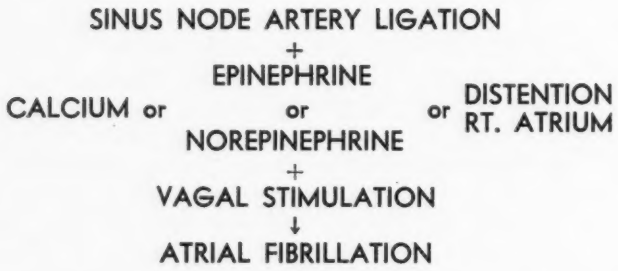

Figure 19

A summary of some experimental observations on atrial arrhythmias in myocardial infarction.

thereby produce a vagomimetic reflex (Marey's reflex).[25] Acute hypertension does sometimes occur during acute myocardial infarction.[38]

Iatrogenic Factors

A number of therapeutic measures commonly employed in patients with acute myocardial infarction may contribute to the onset of atrial arrhythmias. Prominent among these is quinidine. Because it suppresses all myocardial excitability, quinidine may suppress an already weakened sinus node or AV node still further and thereby facilitate atrial arrhythmias. Although this possibility is not a strong contraindication to the use of quinidine otherwise indicated, its effect on the nodal centers should be kept in mind.

The effects of digitalis on the sinus node and AV node depend on the dosage administered. In therapeutic levels it mildly suppresses AV conduction, while in toxic doses it completely blocks it. In therapeutic doses its effect on the sinus node is not clinically significant, but in toxic doses it sometimes produces sinus arrest. In addition to nodal effects, digitalis accelerates repolarization of atrial myocardium,[22, 23] thus increasing the normal disparity of repolarization speed in atrial fibers and favoring the onset of atrial fibrillation. As with quinidine, digitalis should still be employed when indicated in myocardial infarction, but in determining its indication it is well to remember its effects on the conduction centers.

Pressor amines are being employed with increasing frequency in the therapy of acute myocardial infarction with hypotension, and have undoubtedly been responsible for the saving of many lives. However, they too may contribute to the onset of atrial arrhythmias. The two ways in which this may occur are by a chronotropic effect on myocardium (already discussed) and by overshooting the therapeutic mark and producing acute hypertension. A remarkable example of the latter problem was recently reported by Smith and Logue;[39] their emphasis on the vagomimetic reflexes brought into play by their therapy is most important.

Other therapeutic measures may also play a role in iatrogenic facilitation of the onset of atrial arrhythmias, but the ones presented serve to orient thought to these factors.

General Comment

In a recent experimental study on the pathogenesis of atrial arrhythmias in myocardial infarction the validity of most of these clinical considerations was confirmed in the laboratory,[40] and a schematic summary is presented in figure 19. Not one of the factors listed was capable alone of producing atrial fibrillation except in rare circumstances; additionally, any two of the factors also usually failed to induce atrial fibrillation. When the sinus node was made ischemic, and calcium, catecholamines, or atrial distention was added, then vagal stimulation regularly produced atrial fibrillation. It was concluded that this complex combination, employing only factors that are known to occur in the course of

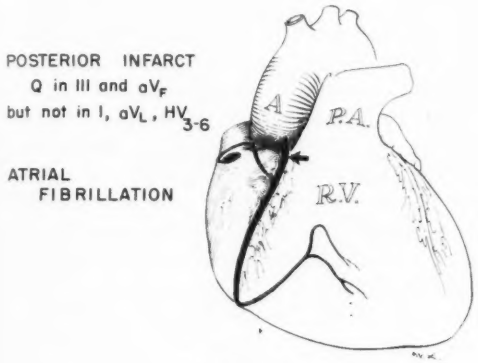

Figure 20

A combination of acute posterior myocardial infarction and atrial fibrillation indicates an occlusion of the first 2 cm. of the right coronary artery.

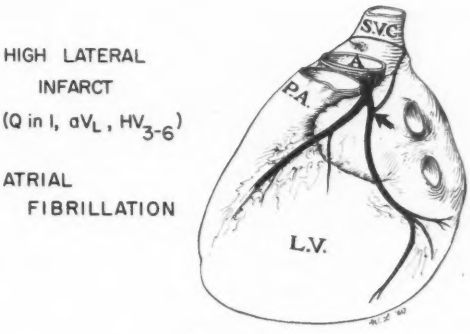

Figure 21

A combination of acute high lateral myocardial infarction and atrial fibrillation indicates an occlusion of the first centimeter of the left circumflex coronary artery and is associated with a grave prognosis.

acute myocardial infarction in man, was a valid demonstration of the true complexity of pathogenesis of atrial arrhythmias in myocardial infarction.

The consistent demonstration of morphologic changes in the sinus node at necropsy of patients dying of acute myocardial infarction with atrial arrhythmias requires special study of the region that is somewhat more detailed than technics conventionally employed in the routine necropsy. Numerous descriptions of the anatomy of the sinus node are available.[41-46] To determine whether a main coronary occlusion is proximal to the origin of the sinus node artery only requires knowledge of the anatomy of the latter vessel,[10, 30] which may arise from the proximal portion of either the right or left circumflex coronary artery.

The frequency of serial sectioning in the region of the sinus node need not be every 5 micra. Sections obtained approximately 2 mm. apart are satisfactory to assure incorporation of significant focal lesions of the node. For the average node this produces about 10 slides, a number that one can conveniently study carefully. Hudson has recently reported a similar experience in "serial" sectioning of the sinus node.[18]

Using the normal anatomy of the coronary arteries in conjunction with the behavior of the ischemic sinus node and AV node, one can determine in vivo the exact location of some acute coronary occlusions. Just as a neurologist is able to determine the location of a cerebral artery occlusion by the abnormal neurologic manifestations, a cardiologist can determine the location of some coronary occlusions from the abnormal behavior of the cardiac conduction centers.

It is well known that most myocardial infarctions occur in hearts with pathology in more than one coronary artery, but some infarctions occur by the occlusion of a single artery. If the atrial arrhythmias of an acute myocardial infaret are due to recent occlusion of one artery with blood supply to the sinus node originating beyond an old occlusion in another artery, finding of infarction in the sinus node (as in every case of this study) suggests that collateral circulation to the node was dependent on patency of the recently occluded artery. Thus atrial arrhythmias during myocardial infarction imply ischemia of the sinus node plus coronary occlusion proximal to the origin of its blood supply, but the occlusion may be either recent or remote. In this regard such reasoning tells neither more nor less than coronary angiography.

The complex problem of multiple coronary occlusions may be more rationally approached if we understand the behavior of myocardial

infarction that follows a single coronary occlusion. The concept of this type of analysis may be introduced by considering right coronary artery occlusion. Since the right coronary supplies the AV node in 90 per cent of human hearts, a patient with acute myocardial infarction who develops any degree of heart block almost certainly has a right coronary occlusion.[47–49] Vagotonia associated with acute infarction may contribute to this block, but this factor is usually more transient.

Determination that the right coronary is occluded still leaves a long segment of vessel in which to localize the occlusion. Of some help is the fact that most clinically recognizable myocardial infarctions are associated with an occlusion in the first 4 or 5 cm. of the artery. Of much greater localizing value, however, is the onset of atrial arrhythmias. This can be detected on clinical auscultation, and confirmed electrocardiographically in all except the most transient cases.

If an atrial arrhythmia occurs in a patient with a posterior myocardial infarction, the coronary occlusion is most likely to be proximal to the origin of the sinus node artery. Since true posterior infarctions are in 90 per cent of cases due to right coronary occlusion, and since the sinus node artery from the right (55 per cent of humans) arises most frequently within 2 or 3 cm. from the aorta, the coronary occlusion in a posterior myocardial infarction with an atrial arrhythmia is most likely in the first 2 or 3 cm. of the right coronary artery (fig. 20).

In the 10 per cent of patients who supply the crux of the heart from the left circumflex artery, a clinically recognizable myocardial infarction is most likely to follow occlusion in the proximal left circumflex artery, which produces not only a true posterior but also a high lateral ventricular infarction. In such a case the electrocardiographic evidence of infarction is not limited to leads III, aV_F, and V_8, but is also seen in aV_L, lead I, and high leads HV_3 to HV_6. Thus posterior infarction when due to left circumflex occlusion may be diagnosed with the use of conventional supplementary electrocardiographic leads. In such cases the added occurrence of atrial arrhythmias serves to localize the occlusion to the very first centimeter of the left circumflex artery, for the sinus node artery from the left (45 per cent of humans) only rarely arises any greater distance from the bifurcation than this (fig. 21). Proximity of such occlusions to the main left coronary artery, and the increased likelihood of eventual occlusion of this main trunk, serves to explain why such a high mortality rate has been described in lateral myocardial infarctions associated with atrial fibrillation,[50] an observation which has previously been unexplained.

From these two basic considerations of occlusions of the right and left circumflex coronary arteries, it is simple to extend the same reasoning to other combinations in the heart. Since the sinus node artery virtually always arises from either the right or left side, not from both, location of an occlusion proximal to this vessel becomes a very useful tool.

It is unusual (less than 10 per cent) for the right coronary artery not to reach the crux of the heart and AV node, and conversely it is unusual for the left circumflex to reach this point; the lengths of these two arteries are reciprocal.[51] Lateral infarctions not associated with atrial arrhythmias suggest that the sinus node artery arose proximal to the point of occlusion in the left circumflex artery, or that the sinus node artery in that case arose from the right side; the latter explanation is the usual one in clinically recognizable infarctions. On the right side, a posterior infarction not associated with atrial arrhythmias suggests that the sinus node artery either arose proximal to the point of occlusion in the right coronary artery or arose from the left side; either of these is equally possible, since the right coronary is usually longer than the left circumflex. It is apparent that the absence of atrial arrhythmias is much less helpful than their presence in localizing a coronary occlusion.

Anteroseptal myocardial infarctions, which in *single* coronary occlusions are almost invariably due to left anterior descending coronary occlusion, are rarely associated with either atrial arrhythmias or heart block. If

AV block occurs, it is usually due to a vagomimetic reflex rather than damage of the AV node. If an atrial arrhythmia occurs there is virtually always an associated second coronary occlusion (old or new) involving the left circumflex or right coronary artery.

Finally, comment is offered regarding the significant differences in canine and human coronary anatomy[10, 30] relative to interpretation of changes in cardiac rhythm in canine experiments on myocardial infarction. The sinus node artery of the dog is nearly always a terminal branch of the right coronary artery, whereas the sinus node artery in man arises with about equal frequency from the right and left sides, and from the anterior third rather than the distal third. The arterial supply of the AV node in the dog is more complex than in man and cannot be so simply analyzed as determining which artery crosses the crux. The left coronary artery of the dog supplies almost the entire left ventricle and interventricular septum, whereas the posterior wall of the left ventricle in man is most often supplied by the right coronary artery. It is unnecessary to go into more detail regarding these differences here. The careful planner of canine experiments on myocardial infarction should be more familiar with them than is commonly the case, however.

Summary

In each of 11 necropsied patients with myocardial infarction and atrial arrhythmias, a coronary occlusion was found proximal to the origin of the sinus node artery and there was infarction of the sinus node.

The multiple factors influencing the onset of atrial arrhythmias during acute myocardial infarction are discussed. Infarction of the sinus node is only one of these factors. Other important ones are ischemia of the AV node, vagal and vagomimetic reflexes, atrial distention, and circulating chronotropic substances.

By combination of a knowledge of the anatomy and pathology of the human coronary arteries with the observation of atrial arrhythmias during acute myocardial infarction, an accurate diagnosis of the point of coronary occlusion can often be made.

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Colloid Goiter and Atherosclerosis

By RONALD A. WELSH, M.D., JACK P. STRONG, M.D., AND HENRY C. MCGILL, JR., M.D.

THE RELATIONSHIP of the thyroid gland to the severity of atherosclerosis in experimental animals has been clearly established,[1] and the effects of hypothyroidism on cholesterol metabolism in man are well known.[2] Although commonly affirmed in textbooks,[3-5] there is still insufficient evidence that hypothyroidism in man aggravates the severity of atherosclerosis.[6] Complementary evidence would be obtained if any disease of the thyroid gland could be correlated with the severity of atherosclerosis in the human. Colloid goiter is an easily recognized abnormality of the thyroid gland that may be associated with either hypothyroidism, hyperthyroidism, or euthyroidism. One report from an area of endemic goiter (Finland) has shown a positive correlation between goiter and death from coronary artery disease.[7] However, other geographic areas in which goiter is frequent, such as Guatemala,[8] have a very low incidence of morbidity and mortality from coronary heart disease,[9] and the average level of advanced atherosclerotic lesions in the same population is very low.[10] Such conflicting data demand further investigation.

A unique opportunity for testing this suspected relationship arose in a study of the thyroid gland in the local population while a study of the natural history of atherosclerotic arterial lesions was in progress. A series of cases became available in which detailed evaluation of the thyroid gland had been carried out by one investigator, and an independent and detailed evaluation of atherosclerotic lesions had been made by two others. The results to be reported here show no consistent relationship between goiter and atherosclerosis.

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Material and Methods

The thyroid glands from 453 necropsied cases above 20 years of age were obtained for study, of which aortas were available in 285 cases and coronary arteries in 265 cases. Both aorta and coronary specimens were obtained from the same patient in 234 of the cases. Arterial specimens were not available in some cases because they were not collected during the entire period of thyroid collection. The necropsies were performed on the Louisiana State University Service of Charity Hospital of Louisiana at New Orleans and at the Coroner's Office of Orleans Parish from January 1958 through November 1959. Charity Hospital is a large general hospital treating patients of the lowest economic status. The Coroner's Office necropsies are performed after all deaths of a suspicious or violent nature, or after those deaths unattended by a physician, so that there is a wider range of economic status represented. Three hundred and twenty-seven of the 453 cases came from Charity Hospital and 103 from the Coroner's Office.

The opened aortas and coronary arteries were fixed in formalin, stained with Sudan IV, and graded by estimating visually the percentage of the intimal surface covered by each of four different types of atherosclerotic lesions (fatty streaks; fibrous plaques; complicated lesions with thrombosis, hemorrhage, or ulceration; and calcified lesions). A severity index was also calculated on each abdominal aorta according to the formula derived by the Committee on Lesions of the Council on Arteriosclerosis of the American Heart Association.[11] In addition, each case was classified as "death due to a complication of atherosclerosis" or "death not due to a complication of atherosclerosis" from the final necropsy diagnoses.

The thyroid glands were classified according to the presence or absence of colloid goiter; diffusely enlarged glands weighing over 35 Gm. and multinodular glands of any size were considered goitrous. A complete description of goiter as seen in this area has been previously described.[12]

Results

The results of arterial grading of the aorta and coronary arteries for both goiter and nongoiter groups between 20 and 79 years of age, further subdivided by sex and race, are given in table 1. Some of the groups show a higher average level of lesions in the goiter group

Table 1

Average Percentages of Intimal Surface Involved by Each Type of Lesion—Aorta and Coronaries, by Age, Sex, Race, and Presence or Absence of Goiter

		Aorta							Aorta								Coronary arteries											
		Goiter present							Goiter absent								Goiter present					Goiter absent						
	Age group in years	Total no. cases	Total surface	Fatty streaks	Fibrous plaques	Complications	Calcifications	Severity index	Total no. cases	Total surface	Fatty streaks	Fibrous plaques	Complications	Calcifications	Severity index		Total no. cases	Total surface	Fatty streaks	Fibrous plaques	Complications	Calcifications	Total no. cases	Total surface	Fatty streaks	Fibrous plaques	Complications	Calcifications	
	20–29								1	23	23				14								2	10	5	5			
	30–39	1	51	46	5			39	5	29	23	6			30		1	16	13	3			3	33	7	26			
White	40–49								14	47	24	18	3	2	48								12	30	11	16	1	2	White
male	50–59	2	36	20	14	2		43	17	54	21	22	5	6	60		2	66	17	27	5	17	15	41	12	23	1	5	male
	60–69	2	38	30	8			30	21	50	20	20	6	4	55		4	47	9	22	2	14	24	48	12	23	2	11	
	70–79	2	72	29	23	6	14	67	7	59	19	19	7	14	61		1	85	16	44	1	24	7	36	17	15		4	
	20–29								9	29	27	1		1	19								7	17	3	3		11	
Negro	30–39	2	43	31	11		1	41	7	30	27	3			25		2	25	14	11			7	18	1	19			
male	40–49	3	30	10	15	4	1	33	14	39	27	12			32		2	41	2	31	2	6	16	23	12	11			Negro
	50–59	4	53	20	23	6	4	45	25	43	21	17	3	2	39		4	55	10	37	2	6	23	37	15	19	1	2	male
	60–69	6	59	28	20	6	5	58	10	37	17	16	2	2	32		6	27	12	11		4	9	41	19	21		1	
	70–79	1															1	24	17	7									
	20–29								2	23	23				17								2						
	30–39	1	15	14	1			20	2	34	31	3			31		1						1	6	6				
White	40–49	1	59	9	40	3	7	71	3	43	32	10		1	41		1	52	11	39		2	4	35	13	21		1	White
female	50–59	1	58	29	29			50	5	46	22	17	2	5	44								4	43	18	23	2		female
	60–69	4	79	11	31	10	27	78	4	62	16	30	3	13	68		3	30	11	14		5	3	16	7	6		3	
	70–79	1	99	10	31	25	33	88	5	63	22	25	4	12	66		1	93	33	39	5	16	5	61	31	27		3	
	20–29								2	22	21	1			19		1	6	6				3	6	6				
	30–39	3	47	41	6			41	10	31	30	1			21		3	18	9	8		1	8	9	8	1			
Negro	40–49	3	24	21	3			20	9	37	24	13			36		4	11	7	4			10	19	13	6			Negro
female	50–59	4	61	35	19	3	4	51	12	65	28	28	4	5	53		2	26	22	4			9	49	22	23	1	3	female
	60–69	7	66	23	31	3	9	59	10	63	25	27	3	8	60		8	50	25	17	1	7	9	69	27	36		6	
	70–79	3	64	24	28	2	10	61	2	60	32	24	1	3	55		3	67	35	24		8	3	47	24	23			

Table 2

Deaths due to a Complication of Atherosclerosis in Goitrous and Nongoitrous Individuals, 50 to 69 Years of Age

	Total cases	Death due to atherosclerosis	Per cent of cases in which death was due to atherosclerosis
White male—Goiter present	8	2	25
White male—Goiter absent	55	14	25
Negro male—Goiter present	18	3	17
Negro male—Goiter absent	49	12	25
White female—Goiter present	8	1	13
White female—Goiter absent	14	5	36
Negro female—Goiter present	18	1	6
Negro female—Goiter absent	34	8	24

(aortic lesions in Negro men, 60 to 69 years); others show less in the goiter group (coronary lesions in Negro men 60 to 69 years); while most groups show essentially no difference between goiter and nongoiter groups. Overall examination of the data discloses no consistent trend in either direction, and the variations in average level of lesions are well within the range of variation that would be expected in small groups of cases.

In table 2 comparison of goitrous and nongoitrous cases shows no tendency of a higher proportion of deaths due to atherosclerosis in cases with goiter. In fact, where there is a difference, it is in the opposite direction. Table 3 shows that there is no tendency of deaths due to atherosclerosis to have a higher incidence of goiter than deaths from all other causes.

Discussion

The pitfalls involved in studying associations between diseases in a death population are well known,[13] and these limitations must qualify all conclusions based on the data presented here. However, there is no way to assess the quality and quantity of atherosclerotic lesions in man other than by examination of the arteries of deceased individuals. One can at least say that, based on data from this source, there is no tendency for goitrous patients to be more susceptible to fatal myocardial infarction; there is no tendency for patients who have died of atherosclerosis to have a higher incidence of goiter, and there is no tendency for goitrous patients to have either more or less atherosclerosis.

Table 3

Occurrence of Goiter in Atherosclerotic Deaths and Nonatherosclerotic Deaths, Indivduals 50 to 69 years of age

		Total no. cases	No. cases with goiter	Percentage cases with goiter
White male	Deaths due to atherosclerosis	16	2	13
	Deaths not due to atherosclerosis	47	6	12
Negro male	Deaths due to atherosclerosis	15	3	20
	Deaths not due to atherosclerosis	52	15	29
White female	Deaths due to atherosclerosis	6	1	17
	Deaths not due to atherosclerosis	16	7	44
Negro female	Deaths due to atherosclerosis	9	1	11
	Deaths not due to atherosclerosis	43	17	40

The convincingly negative results obtained from our own material led us to review the factual basis for the belief that myxedema accelerates atherosclerosis. The reports usually cited in support of the association between hypothyroidism and atherosclerosis are summarized below.

Barling[14] (1886) described considerable atheroma of the aorta in a stout old woman with myxedema. Hun and Prudden (1888)[15] described two cases of myxedema at necropsy; the usual coronary and aortic lesions were present in the coronary arteries and aorta of a 57-year-old woman, and no description of the arteries was given in the other case. Marchand (1906)[16] found severe aortic calcifi-

cation in a 35-year-old woman with hypothyroidism. Fishberg (1924)[17] reported marked atherosclerosis in the coronary arteries and aorta of a 21-year-old hypertensive patient with myxedema. Wegelin (1925)[18] described severe aortic and coronary lesions in a 56-year-old cretin. Heine (1924)[19] reported mild coronary arteriosclerosis in a 79-year-old hypothyroid patient. Hoelzer (1939)[20] described extensive medial calcification in a 2-year 9-month-old athyreotic child.

Most of these classical references are reports on one or two necropsied cases of untreated hypothyroidism without any comparison with age and sex-matched, euthyroid cases. When age and sex are taken into account, practically all these cases can be considered to be well within the range of variation for the general North American and European population. The case reported by Hoelzer appears to be an arterial disease different from the usual form of atherosclerosis. The presence of severe hypertension in the case reported by Fishberg makes untenable any inference that the severe atherosclerosis was due to hypothyroidism. All these cases, therefore, may be dismissed singly and collectively as insufficient evidence. Kurland and Freedberg[21] have recently reviewed the interrelation of thyroid function to atherosclerosis.

On the other hand, Kountz,[22] in 1950, was unable to show a difference in either intimal or medial arterial lesions between seven patients with low basal metabolic rates and six with normal rates. Four other cases in which the thyroid gland had been completely removed had medial degeneration but no increased intimal disease. Andrus,[6] in 1953, stated "although the literature contains some very dogmatic statements to the effect that myxedema and coronary artery disease are frequently if not invariably associated, there are few reported instances of untreated myxedema in man in which the arterial system has been carefully examined." He cited studies of the Committee of the Clinical Society of London on myxedema, which concluded that myxedema provokes no unusual degree of arterial lesions. Blumgart et al.,[23] in 1952, reported that arteries of eight patients rendered hypothyroid for therapeutic purposes were not different from the arteries of euthyroid patients. Volkstadt,[24] in 1957, found no difference in atherosclerosis between goitrous and nongoitrous patients in 100 necropsied adults between 20 and 80 years of age.

Quite in contrast to the above findings and to our own, Uotila and associates in Finland[7] in 1960, reported a high positive correlation between nodular goiter and death due to coronary occlusion. Goiter was much more frequent in 250 cases of deaths due to coronary occlusion than it was in 250 age and sex-matched accidental death controls. The extent and severity of the coronary artery lesions was not quantitated as in the present study. Reconciliation of these results with our findings appears impossible with the information presently available. It is conceivable that goitrous thyroid glands in Finland function differently from goitrous thyroid glands in New Orleans; this possibility suggests the value of carrying out similar comparisons in other areas where goiter is endemic. Even though in some areas it should be conclusively demonstrated that goiter is associated with increased atherosclerosis, the mechanism is not necessarily reduced thyroid function; both diseases might well be the result of a single etiologic factor acting directly on each organ system.

The presence of goiter, of course, does not necessarily mean that the thyroid gland is functioning at less than normal capacity; any goitrous case may have been hyperthyroid, hypothyroid, or euthyroid. There is little doubt that hypothyroidism in experimental animals aggravates cholesterol-induced arterial lesions, but species variation and the relationship of experimental animal lesions to human atherosclerotic lesions prohibit the categorical transference of these results to man. In view of the present use of thyroid hormone analogues to reduce serum cholesterol with the hope of reducing atherosclerosis, it is important that studies be designed that will conclusively answer the question of the relationship of reduced thyroid function itself to atherosclerotic arterial lesions. These

studies will require the long-term follow up of cases with reduced thyroid function, serial measurement at intervals of thyroid function by laboratory methods, and measurement of the atherosclerotic arterial lesions in these patients as compared with euthyroid patients of the same age, sex, race, and geographic location.

Summary

The thyroid glands from 453 patients 20 to 79 years of age from the New Orleans area were classified according to the presence of colloid goiter, and the coronary arteries and aortas from these same patients were independently graded for atherosclerotic lesions. There was no correlation between colloid goiter and atherosclerosis; nor was there any difference in the percentages of deaths from atherosclerosis in goitrous patients as compared to nongoitrous patients. Because goiter may differ in its functional manifestations from one geographic area to another, and because one group of investigators in Finland has reported a strong association between the two diseases, similar studies should be conducted in other areas. The subject of increased severity of atherosclerosis in human hypothyroidism was reviewed, and it was concluded that the presently recorded data are not adequate to establish a positive relationship.

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Surgical Anatomy of the Coronary Artery Distribution in Congenital Heart Disease

By KEITH REEMTSMA, M.D., CHARLES G. LONGENECKER, M.D., AND OSCAR CREECH, JR., M.D.

DURING the initial phases in the development of open-heart surgery, problems related to the perfusion procedure were common causes of morbidity and mortality. With improved perfusion technics and increased knowledge of the physiology of cardiopulmonary bypass, such problems have become less frequent. Now that the perfusion procedure itself is accomplished with considerable safety, the surgical anatomy of congenital cardiac malformations has assumed increasing importance. The gross anatomic features of various cardiac deformities were elucidated largely before the advent of open-heart surgery, and the pertinent anatomy of the cardiac conduction system has been the subject of several recent studies.[1-5] The coronary artery distribution in congenital heart disease has received scant attention,[6] although recent reports attest to the importance of anomalies of coronary circulation encountered during open-heart surgery.[7-9]

The present report deals with distribution of the coronary arteries in congenital heart disease, with emphasis on the two areas most frequently attacked during open-heart surgery: the right ventricular outflow tract and the region surrounding septal defects.

Materials and Methods

Studies were performed on 154 hearts with congenital malformations and 24 normal human hearts. Coronary arteries of fresh specimens were injected with barium-latex or lead-vinylite suspension. Roentgenograms were made of the unopened and opened hearts, and the specimens were subsequently cleared and photographed. Gross dissection of the major coronary vessels was performed on formalin-fixed hearts.

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Supported by grant H-3545, National Heart Institute, U. S. Public Health Service, and the Louisiana Heart Association.

Results

The ventricular septum in normal and malformed hearts received a generous blood supply from branches of the anterior and posterior descending arteries (fig. 1). The artery to the atrioventricular node arose from the right coronary artery in approximately 90 per cent of cases and from the left coronary in the remaining 10 per cent. This artery originated at a sharp U-shaped turn of the right or left coronary artery near the coronary sinus.

In ostium primum defects the artery to the atrioventricular node lay in a vulnerable position beneath the inferior (dorso-caudad) margin of the defect (fig. 2). Secundum defects, however, were well removed from the blood supply to the conduction system (fig. 3). Most ventricular septal defects, including the ventricular component of atrioventricular canals, lay anterior (ventral) to the main artery to the atrioventricular node, although small vessels in the area of the bundle branches coursed in the ventricular septum immediately beneath the defects (fig. 4).

The right ventricular outflow tract in normal hearts was supplied by small branches of the anterior descending artery and preventricular branches of the right coronary artery. The usual site of right ventriculotomy lay in an avascular area of the normal heart; however, in tetralogy of Fallot, marked increase in vascularity was observed in the right ventricular outflow tract.[10] Less striking increases in vascularity were observed in cases of ventricular septal defect and isolated pulmonic stenosis.

Occasionally major coronary vessels were

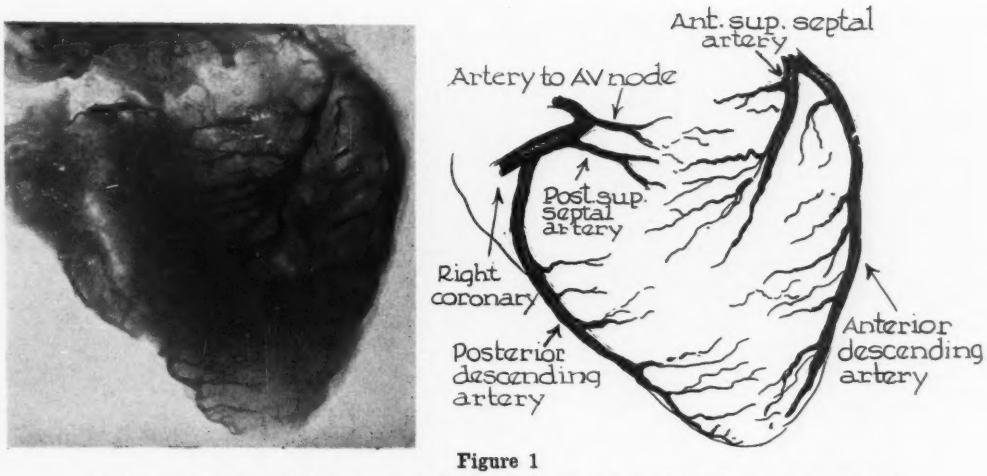

Figure 1

Photograph and drawing of an injected and cleared specimen of the ventricular septum of a normal heart. The septum receives a generous supply from the anterior descending artery of the left coronary and the posterior descending artery from the right coronary. The artery to the atrioventricular node arises at a sharp bend in the right coronary artery.

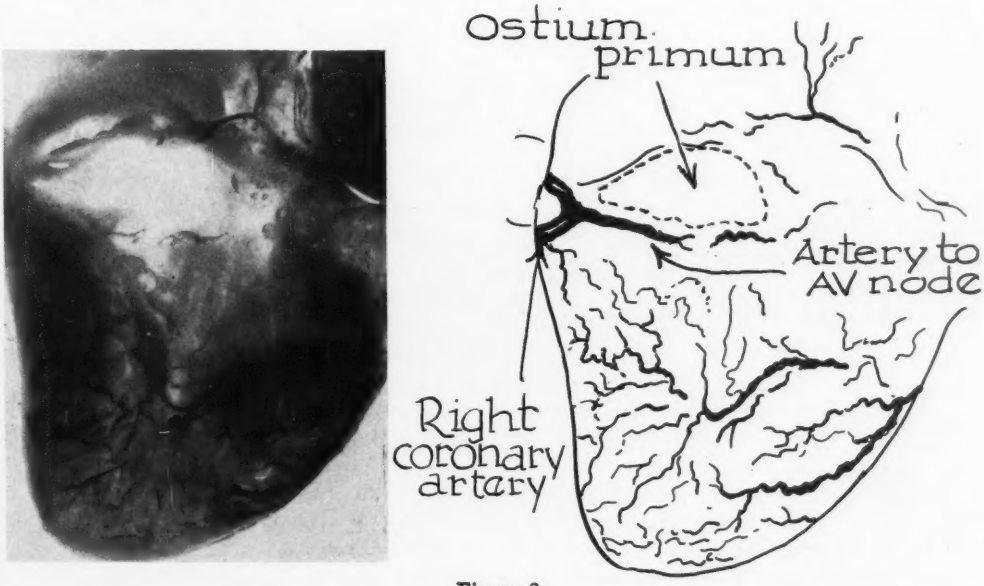

Figure 2

Photograph and drawing of an injected and cleared specimen with an ostium primum type of atrial defect. The artery to the atrioventricular node is seen to course immediately beneath the inferior (dorso-caudad) rim of the ostium primum defect.

found to pass across the right ventricular outflow tract, in the area usually incised during right ventriculotomy. The anterior descending artery occasionally arose from the right rather than the left coronary artery (fig. 5). This anomaly was observed especially in cases of tetralogy with marked dextroposition of the aorta.

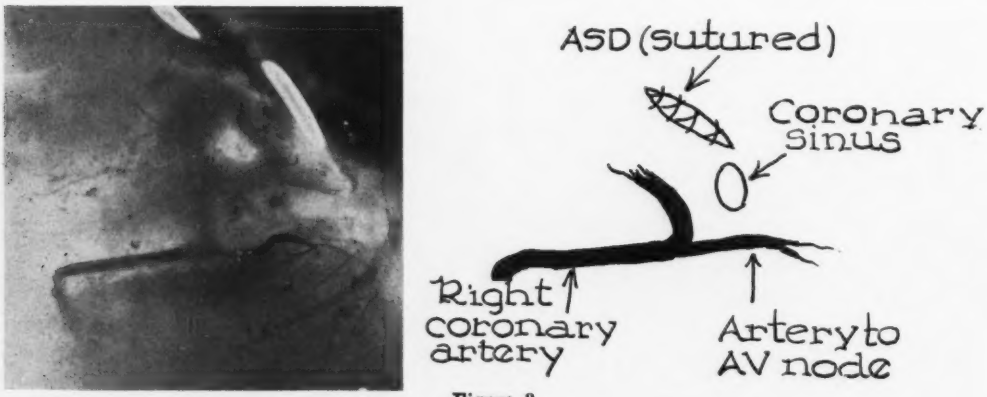

Figure 3

Photograph and drawing of an injected and cleared specimen with an atrial septal defect of the secundum type. The defect, which has been sutured in this instance, lies superior to the artery to the atrioventricular node.

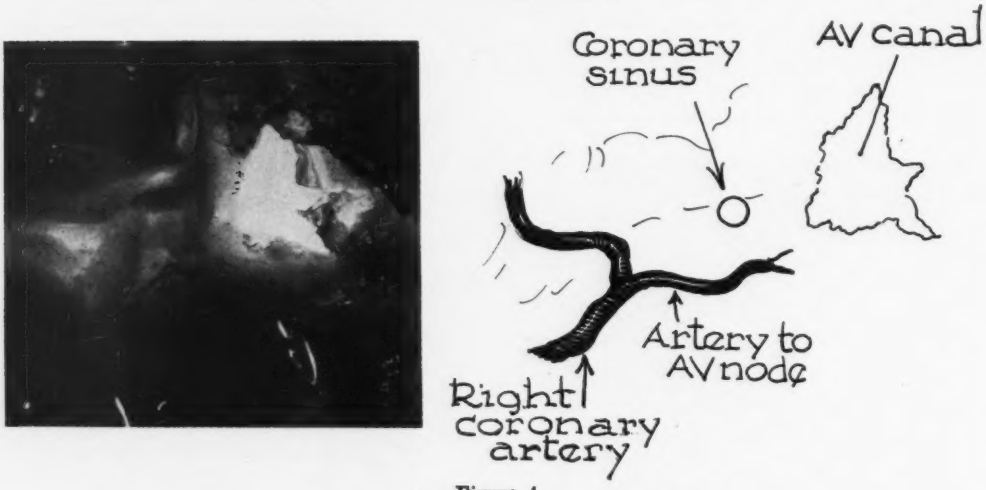

Figure 4

Photograph and drawing of an injected and cleared specimen with atrioventricular canal defect. This defect lies anterior to the main artery to the atrioventricular node.

A variant of single coronary artery of particular importance was the single right coronary artery in which the entire left coronary branch passed in front of the pulmonary artery (fig. 6). A similar situation was observed in one instance in which the left coronary, after arising from the left sinus of Valsalva, passed in front of rather than behind the pulmonary artery (fig. 7).

In most instances of anomalous distribution of vessels in the area of the right ventricular outflow tract, external examination of the heart revealed the presence of a major vessel in an abnormal location. In occasional instances, however, a major coronary vessel was buried within the myocardium and would not have been apparent on gross examination at the operating table.

Discussion

Anomalies of the coronary arteries are generally considered of no clinical significance, except in such conditions as coronary artery origin from the pulmonary artery and coro-

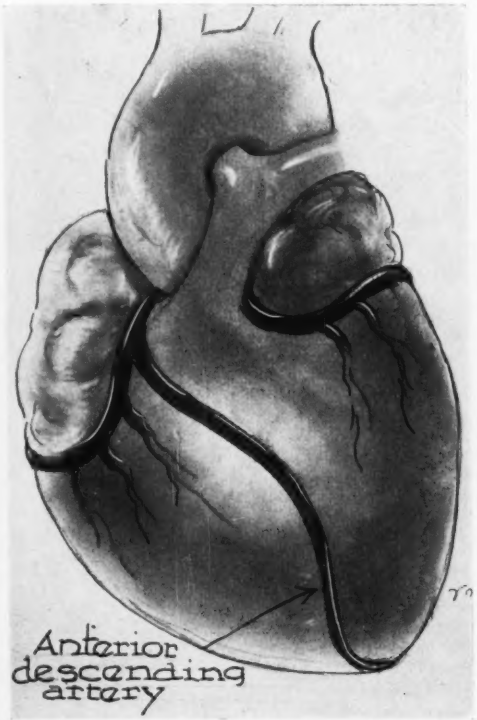

Figure 5

Drawing of a heart showing the anterior descending artery arising from the right coronary artery. The anterior descending artery in this instance crosses the outflow tract of the right ventricle.

nary arteriovenous, arterio-atrial, or arterioventricular fistulas. In open-heart surgery, however, the distribution of major coronary arteries may assume crucial importance. The artery to the atrioventricular node is a constant vessel arising from the left or right coronary artery in the area of the coronary sinus. This vessel lies in a vulnerable position immediately beneath the inferior (dorsocaudad) rim of ostium primum defects. Smaller vessels, from both the right and left coronary arteries, accompany the bundle branches. Whether postoperative conduction disturbances are related to direct injury to the conduction system, to compromise of its blood supply, or to other factors remains conjectural.

There is no doubt, however, about the importance of anomalous distribution of the

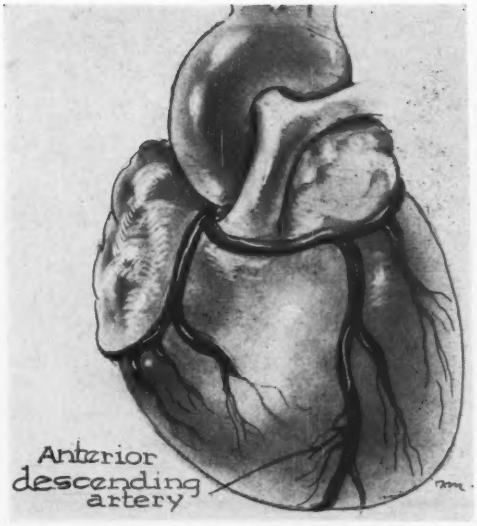

Figure 6

Drawing of a specimen with a single right coronary artery. The left coronary branch arises from the single right coronary artery and passes in front of the pulmonary artery, across the right ventricular outflow tract.

coronary vessels in the region of the right ventricular outflow tract. In the most dangerous forms, either the anterior descending artery or the entire left coronary artery passes across the right ventricular outflow tract.

Senning[7] reported five cases with a major anomalous vessel in this region. In two cases the anterior descending artery originated from the right coronary artery and coursed across the infundibulum. He reported one case in which the entire left coronary arose from the right coronary and coursed across an area of infundibular stenosis within the myocardium. The patient died immediately following division of this vessel.

In a summary of cases of tetralogy treated by open repair, Kirklin and associates[8] described four instances of anomalous vessels in the region of the right ventricular outflow tract. In one instance a large vessel, presumably the left coronary, arose from a single right coronary artery. Its division during ventriculotomy resulted in death. In three cases the anterior descending artery arose from the right coronary. In one of these cases

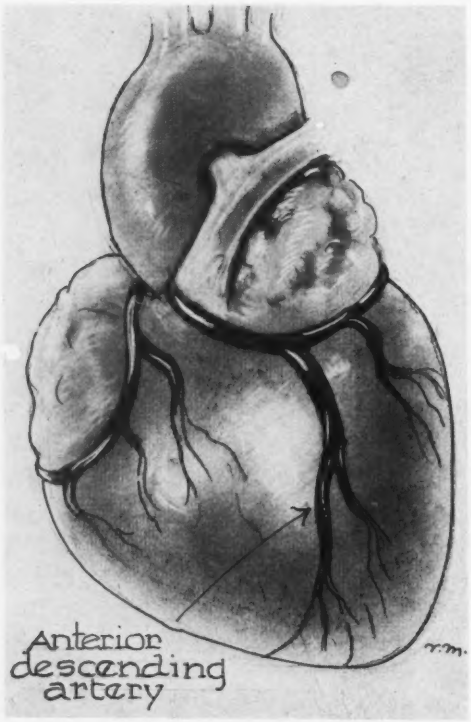

Figure 7

Drawing of a specimen with tetralogy of Fallot in which the left coronary artery arose from a normal site in the aorta but passed anterior to the pulmonary artery.

this branch was divided, with subsequent death of the patient due to infarct of the left ventricle. Friedman and associates[9] reported a fatality following division of the left coronary artery which crossed the right ventricular outflow tract after arising from a single right coronary artery.

These anomalies in the region of the right ventricular outflow tract appear most frequently in transposition complexes and tetralogy with marked dextroposition of the aorta. The pertinent embryology of this malformation, elucidated by Spitzer[11] and Lev,[12] has recently been reviewed.[10]

Summary

Distribution of major coronary arteries was studied in 154 congenitally malformed hearts and 24 normal hearts.

The artery to the atrioventricular node constantly arose in the area of the coronary sinus from either the right or left coronary artery. In specimens with ostium primum malformations, this artery coursed immediately beneath the inferior (dorso-caudad) rim of the defect.

Anomalous distribution of the coronary arteries in the region of the right ventricular outflow tract poses a serious problem in open-heart surgery. The two most frequent variants were anomalous anterior descending artery arising from the right coronary, and single right coronary artery with the left coronary branch passing across the right ventricular outflow tract.

Such anomalies occur most frequently in transposition complexes and tetralogy with extreme dextroposition of the aorta. Fatalities have been reported following division of these vessels.

Although some anomalies of the coronary vessels may be recognized on inspection of the heart at the operating table, a major vessel may lie buried within the myocardium.

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Thomas Sydenham
1624–1689

He that designs to attain to the right understanding of any Art or Profession, usually chooses some Eminent Man of the Art to be his Guide and Pattern, by whose Directions and Example, join'd with a tolerable Capacity, and sufficient Diligence, he is, and is deem'd, at a stated Period, legally qualified for the exercise of the Art he professes. And this I Take to be the best and readiest way of attaining to the knowledge of any Art.

But seeing by the Custom of our Country, Physicians are educated another way, and chiefly improve themselves by Study and Books, it behooves them to make choice of such Authors as have been much conversant in Practice, and are generally accounted Candid and Sincere. In the first Rank of these I place this Author who was peculiarly disposed for Practice, and a Vein of Sincerity runs through his whole Works, a thing very rare in Physical Authors, especially in the Modern; and for this reason it was, he was so much calumniated by ill Men.

This Worthy Man was always busied in improving the Practice of Physick, even then when he was stepping on the Threshold of the other World, and like the Great Archimedes, would not suffer himself to be interrupted by any thing but resistless Fate.

He died in the Sixty sixth year of his Age; A great Age it was for one that had been closely besieged, near half the time with Opprobrium Medicorum, the Gout; which finding its frequent Efforts repell'd by his great Skill, called in its Auxiliary, the Stone, and together, with much a-do, they storm'd the tottering Tenement of Clay, when by reason of Age it was Scarce Tenible any longer.

He was born in Dorsetshire: His Father was a Gentleman of good Reputation, and a plentiful Estate. He was educated in All-Souls College in Oxford, and was Fellow of the same, and afterwards a Member and Ornament of the College of Physicians in London.

He was Religious, Loyal, Learned, of a Solid Judgment, and Sterling Honesty: But I shall say no more of him, his Book will be the best and most lasting Monument of his Fame.

The Antihypertensive Mechanisms of Salt Depletion Induced by Hydrochlorothiazide

By BERTRAM M. WINER, M.D.

AN ANTIHYPERTENSIVE effect attends daily administration of a low-sodium diet, a benzothiadiazine, a mercurial, or an aldosterone antagonist.[1-6] These measures have in common the induction of a sodium deficit. In the nonedematous hypertensive patient, 1 or 2 liters of extracellular fluid are lost, and plasma volume is reduced.[2, 6] Following the diuresis the pressor response to norepinephrine is decreased and the depressor response to ganglion-blocking agents increased.[7-12]

The hemodynamic effects of the induced oligemia have been considered by some investigators to account wholly or in large part for the antihypertensive effects of salt depletion.[2, 4, 9, 10, 13] However, several observations oppose this concept. Plasma volume and cardiac output are reduced in the first week of administration of a benzothiadiazine,[13-15] but within a month the plasma volume deficit becomes small and cardiac output is no longer decreased.[16] Within 6 months plasma volume may return to pretreatment levels, although the antihypertensive effects persist.[17] Re-expansion of plasma volume by intravenous administration of Dextran or plasma returned the basal blood pressure and the response to a ganglion-blocking agent to control levels in some studies,[2, 4, 9] but not in others.[5, 6, 12]

This report summarizes studies designed to elucidate the mechanisms by which the basal blood pressure and the blood pressure responses to pressor and depressor substances are affected by a benzothiadiazine.

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Supported by grants no. H-1835 and H-6119 from the National Heart Institute, U. S. Public Health Service, and by grant no. 446 from the Massachusetts Heart Association.

Materials and Methods

Nine of the 10 patients studied had essential hypertension. The tenth patient (H.F.) had chronic glomerulonephritis. All had grade two fundi (Keith-Wagener scale). None showed evidence of congestive heart failure. Dietary sodium was not restricted.

The basal blood pressure, the pressor response to norepinephrine, and the depressor responses to trimethapan, erythrol tetranitrate, and protoveratrine B were determined in four periods of study. In the first period a placebo was administered for at least 4 weeks. Hydrochlorothiazide was given as the sole long-term antihypertensive measure in daily doses of 150 mg. in the subsequent periods of study. The basal blood pressure and the responses to the vasoactive substances were re-examined after 2 weeks of hydrochlorothiazide therapy. The effects of re-expansion of plasma volume by Dextran were then studied. Five hundred milliliters of 6 per cent Dextran in 5 per cent glucose in water were infused intravenously at a rate of approximately 20 ml. per minute. Ninety minutes later the blood pressure and responses to vasoactive drugs were determined. Upon completion of these studies 20 Gm. of sodium chloride were added daily for a week, at which time the responses were again examined.

The following procedures were carried out in each period of study. All blood pressures were determined by the auscultatory technic by the same technician in the laboratory. The blood pressure was measured in the recumbent position at intervals of a few minutes for at least 30 minutes before addition of a pressor or depressor drug. The lowest two blood pressures were averaged to represent the basal blood pressure. The pressor response to norepinephrine was determined during an intravenous infusion administered at a rate of 5.5 mcg. per minute for 10 minutes by a constant infusion pump. An average of the blood pressures obtained at intervals of a minute from the sixth to tenth minutes was taken to represent the

Table 1

The Basal Blood Pressure during a Placebo and after Hydrochlorothiazide with and without Dextran or Salt

	Blood pressure, mm. Hg			
Patient	Placebo	Hydrochlorothiazide	Hydrochlorothiazide and Dextran	Hydrochlorothiazide and Salt
P.G.	209/118	196/108	202/105	214/116
H.F.	203/112	191/102	205/91	216/114
I.F.	210/112	179/94	181/98	196/109
M.F.	243/112	201/104	213/100	223/101
S.G.	183/114	176/103	178/105	194/110
M.K.	173/105	150/97	176/103	172/103
I.R.	177/113	160/107	169/104	169/105
J.A.	211/108	154/92	175/108	215/114
R.R.	197/98	167/99	179/99	191/104
F.B.	211/113	181/101	178/106	211/116
Mean	202/111	176/101	186/102	200/109
Mean change from placebo period		−26/−10	−16/−9	−2/−2
Standard deviation		15/5	15/7	11/6
p		<.001/<.001	<.01/<.01	>.1/>.1
Mean change from preceding period of study			+10/+1	+14/+7
Standard deviation			9/7	13/7
p			<.01/>.1	<.01/<.01

Table 2

The Response to Norepinephrine during a Placebo and after Hydrochlorothiazide with and without Dextran or Salt

	Blood pressure, mm. Hg			
Patient	Placebo	Hydrochlorothiazide	Hydrochlorothiazide and Dextran	Hydrochlorothiazide and Salt
P.G.	226/128	216/114	219/118	216/125
H.F.	224/130	217/114	229/100	229/118
I.F.	252/131	228/113	208/120	258/126
M.F.	267/121	216/109	235/109	243/106
S.G.	220/124	200/118	198/108	211/121
M.K.	208/120	184/106	202/106	210/115
I.R.	210/131	205/120	207/120	206/122
J.A.	275/128	222/112	202/111	260/126
R.R.	224/112	194/105	202/103	224/116
F.B.	255/124	205/108	211/119	234/122
Mean	236/125	209/112	211/111	229/120
Mean change from placebo period		−27/−13	−25/−1	−7/−5
Standard deviation		18/4	24/7	11/5
p		<.01/<.001	<.01/<.001	>.05/<.02

response. Ten minutes after the end of this infusion, a continuous intravenous infusion of trimethapan was given at a rate of 1.0 mg. per minute for 10 minutes; the response was determined as the average blood pressure in the sixth to tenth minutes of infusion. The rate of administration was then increased to 1.6 mg. per minute for 20 minutes; the response was calculated as the average blood pressure of the eleventh to twentieth minutes. Forty-five minutes after completion of this infusion, at a time when the blood pressure in the recumbent and standing positions had returned to the original levels, protoveratine B was administered intravenously in a dose of 135 or 160 meg. in a period of 2 minutes. The blood pressures from the eleventh to twentieth minutes were

Table 3

The Relative Increments of Response to Norepinephrine

Patient	Per cent rise in systolic pressure*		Per cent rise in diastolic pressure*	
	Placebo	Hydrochlorothiazide	Placebo	Hydrochlorothiazide
P.G.	8	10	8	6
H.F.	10	14	16	12
I.F.	20	27	17	20
M.F.	10	7	8	5
S.G.	20	14	9	15
M.K.	20	23	14	9
I.R.	19	28	16	12
J.A.	30	44	19	22
R.R.	14	16	14	6
F.B.	21	13	10	7
Mean	17.2	19.6	13.1	11.4
Mean change from placebo period		+2.4		−1.7
Standard deviation		6.8		4.3
p		>.1		>.1

*Calculated as (pressure during infusion of norepinephrine minus the pre-infusion pressure) × 100, divided by the pre-infusion pressure.

averaged to represent the response. The response to 15 mg. of erythrol tetranitrate sublingually was studied on a separate day. Blood pressures were determined in the sitting position and after 2 minutes of standing at intervals of a few minutes for 30 minutes before and 2 to 6 hours after administration of erythrol tetranitrate; the average blood pressure 45 to 90 minutes after administration was taken to represent the response.

During continued administration of hydrochlorothiazide, the response to norepinephrine was reexamined after return of blood pressure by an infusion of angiotensin II to the original levels observed prior to hydrochlorothiazide therapy. Ninety minutes after intravenous administration of 500 ml. of 6 per cent Dextran in 5 per cent glucose in water, angiotensin II was given intravenously at a rate determined in the individual patient to return the blood pressure approximately to the levels of the placebo period of study. During continuation of the infusion of angiotensin II norepinephrine was added intravenously for 10 minutes at a rate of 5.5 meg. per minute by a second constant infusion pump. The average blood pressure during the sixth to tenth minutes was taken to represent the response.

Results

Effects of Hydrochlorothiazide

The blood pressure was significantly lower during administration of hydrochlorothiazide

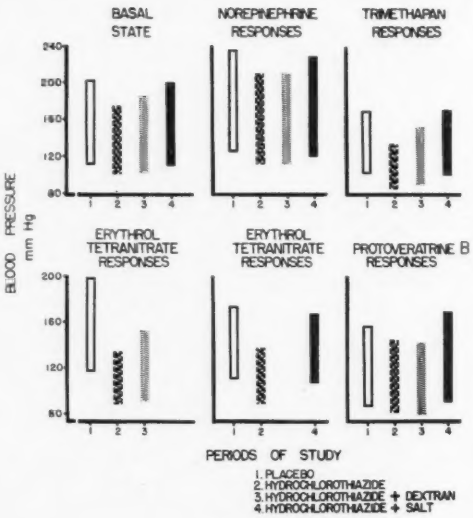

Figure 1

The mean values of the basal blood pressures and the blood pressure responses to norepinephrine, trimethapan, erythrol tetranitrate, and protoveratrine B during oral administration of a placebo and during hydrochlorothiazide therapy with and without added Dextran or salt.

than during administration of a placebo ($p <$ .001) (table 1). Systolic pressure fell an average of 13 per cent and diastolic an average of 9 per cent.

Intravenous infusion of norepinephrine at a rate of 5.5 meg. per minute was followed by a pressor response in each case during administration of a placebo or hydrochlorothiazide. The absolute levels of blood pressure during infusions of norepinephrine were lower in the diuretic than in the placebo period of study (table 2). However, the relative increments of response to norepinephrine, calculated in terms of per cent change in systolic and diastolic pressure, were not affected by hydrochlorothiazide (table 3).

Continuous intravenous infusion of trimethapan lowered the blood pressure of each subject during the placebo and diuretic periods of study. Systolic and diastolic pressures during infusions of trimethapan were significantly lower during administration of hydrochlorothiazide than during the placebo period (table 4).

Table 4

Response to Trimethapan during a Placebo and after Hydrochlorothiazide with and without Dextran or Salt

Patient	Blood pressure, mm. Hg			
	Placebo	Hydrochlorothiazide	Hydrochlorothiazide and Dextran	Hydrochlorothiazide and Salt
Infusion at rate of 1.0 mg. per minute				
P.G.	179/115	145/96	158/97	166/101
H.F.	179/98	125/74	182/75	194/106
I.F.	178/107	144/88	149/90	177/96
M.F.	150/82	102/68	126/73	164/82
S.G.	162/98	151/94	146/86	170/105
M.K.	160/100	150/96	164/96	161/101
I.R.	147/95	115/77	143/91	153/100
F.B.	192/110	134/86	148/95	165/98
Mean	168/101	133/85	152/88	169/99
Mean change from placebo period		−35/−16	−16/−13	+1/−2
Standard deviation		18/8	17/7	14/9
p		<.001/<.001	<.05/<.01	>.1/>.1
Infusion at rate of 1.6 mg. per minute				
P.G.	135/90	126/87	135/89	138/89
I.F.	150/91	130/85	134/77	168/96
M.F.	104/66	82/60*	102/65	141/76
S.G.	131/80	102/67	113/74	124/76
M.K.	147/99	122/85	150/94	144/95
I.R.	133/94	100/69	140/90	155/104
J.A.	189/95	107/66	131/75	197/104
F.B.	170/98	106/67	137/94	158/100
Mean	145/89	109/73	130/82	153/93
Mean change from placebo period		−36/−16	−15/−7	+8/+4
Standard deviation		25/11	22/7	17/6
p		<.01/<.01	>.05/<.02	>.1/>.1

*Infusion discontinued at 4 minutes because of hypotension.

Erythrol tetranitrate had a modest hypotensive effect during the administration of a placebo. Systolic and diastolic pressures after erythrol tetranitrate were significantly lower in the diuretic than in the placebo period of study (table 5); the effect was greater in the standing than the sitting position. The onset of the response occurred within 20 minutes and the maximal response within 1 to 2 hours. Blood pressure returned to control levels within 3 to 6 hours.

Single intravenous injections of 130 to 160 mcg. of protoveratrine B were hypotensive in each case during placebo and hydrochlorothiazide administration. A depressor response appeared within a few minutes and was maximal within 11 to 20 minutes. The diastolic pressure after administration of protoveratrine B was lower in the diuretic than in the placebo period of study ($p < .01$) although the systolic responses in the two periods of study did not differ significantly (table 6).

Effects of Re-expansion of Plasma Volume

Systolic pressure rose significantly after the intravenous infusion of Dextran, but remained at a significantly lower level than that of the placebo period (table 1). Diastolic pressure was not affected by the infusion of Dextran.

After re-expansion of plasma volume, the decreases in systolic pressure during infusions of trimethapan (table 4) and after sublingual administration of erythrol tetranitrate (table 5) were intermediate between those observed during administration of a placebo and those

Table 5

Response to Erythrol Tetranitrate during a Placebo and after Hydrochlorothiazide with and without Dextran or Salt

Patient	Blood pressure in standing position, mm. Hg			
	Placebo	Hydrochlorothiazide	Hydrochlorothiazide and Dextran	Hydrochlorothiazide and Salt
P.G.	218/136	116/90		176/123
H.F.	166/111	118/70		215/112
S.G.	167/109	168/100		168/106
M.K.	160/99	130/83		144/97
I.R.	155/114	156/104		151/109
J.A.	179/103	132/86		163/103
R.R.	182/101	144/93		154/102
Mean	175/110	138/89		167/107
Mean change from placebo period		−37/−21		−8/−3
Standard deviation		35/16		29/5
p		<.05/<.02		>.1/>.1
P.G.	218/136	116/90	129/101	
H.F.	166/111	118/70	150/85	
J.A.	179/103	132/86	126/89	
R.R.	182/101	144/93	155/84	
M.F.	245/129	166/104	206/98	
Mean	198/116	135/89	153/91	
Mean change from placebo period		−63/−27	−45/−25	
Standard deviation		27/16	28/9	
p		<.01/<.02	<.05/<.01	

during hydrochlorothiazide in the absence of expansion of plasma volume. Expansion of plasma volume did not reverse the effects of hydrochlorothiazide on the diastolic responses to trimethapan and erythrol tetranitrate.

The effect of protoveratrine B on both systolic and diastolic pressures was greater during combined administration of hydrochlorothiazide and Dextran than in the control period (table 6).

Infusion of Dextran did not affect the pressor response to norepinephrine (table 2).

Effects of the Addition of Salt

The ingestion of 20 Gm. of sodium chloride daily during hydrochlorothiazide therapy obliterated the effects of hydrochlorothiazide on basal systolic and diastolic pressure and on the responses of systolic and diastolic pressure to trimethapan, erythrol tetranitrate, and protoveratrine B (tables 1 and 4–6). The diastolic response to norepinephrine remained slightly reduced ($p < .02$).

The mean values of the basal blood pressure and the blood pressure responses to norepinephrine, trimethapan, erythrol tetranitrate, and protoveratrine B during administration of (1) a placebo, (2) hydrochlorothiazide, (3) hydrochlorothiazide and added Dextran, and (4) hydrochlorothiazide and added salt are shown graphically in figure 1.

Effect of Angiotensin II on the Response to Norepinephrine

The response to intravenously infused norepinephrine was examined in eight patients during long-term administration of hydrochlorothiazide after re-expansion of plasma volume by Dextran and the subsequent addition of a continuous intravenous infusion of angiotensin II at a rate determined to return the blood pressure approximately to the original hypertensive levels of the placebo period of study (table 7). The amounts of angiotensin II required to restore the blood pressure to the original levels averaged 0.3 mcg. per

Table 6

Response to Protoveratrine B during a Placebo and after Hydrochlorothiazide with and without Dextran or Salt

Patient	Dose mcg.	Blood pressure, mm. Hg			
		Placebo	Hydrochlorothiazide	Hydrochlorothiazide and Dextran	Hydrochlorothiazide and salt
P.G.	160	120/96	108/67	116/66	158/85
H.F.	160	200/105	181/86	175/89	212/101
I.F.	160	156/91	158/89	168/80	185/98
M.F.	160	168/83	180/95	169/78	190/88
S.G.	160	171/83	163/97	145/82	162/95
M.K.	135	142/83	133/80	119/74	154/89
I.R.	135	129/89	113/76	111/71	137/88
F.B.	160	163/89	131/81	129/88	150/82
Mean		156/87	146/81	142/79	169/91
Mean change from placebo period			−10/−6	−14/−8	+13/+4
Standard deviation			13/10	16/6	18/7
p			>.05/<.01	<.05/<.01	>.05/>.1

minute, with a range of 0.1 to 0.5 mcg. per minute. The response to norepinephrine under these circumstances was similar to that observed during the administration of a placebo (table 7).

Discussion

Previous studies in this laboratory have shown that after 2 to 4 weeks of benzothiadiazine therapy the addition of 500 ml. of 6 per cent Dextran in 5 per cent glucose in water returned plasma volume to levels slightly above those in the control period. Systolic pressure rose but did not reach control levels; diastolic pressure was unaffected.[6] These observations suggested that hypovolemia does not fully account for the antihypertensive effect or benzothiadiazines. This conclusion is supported by the present studies. The addition of Dextran during hydrochlorothiazide administration modified the basal systolic pressure and the responses of systolic pressure to trimethapan and erythrol tetranitrate, but did not reverse the diuretic-induced changes in basal diastolic pressure, systolic responses to norepinephrine or protoveratrine B, or diastolic responses to the four vasoactive substances studied. When it was affected, the systolic pressure rose to levels intermediate between those before and during benzothiadiazine therapy.

Oligemia is associated with reduced cardiac output. Cardiac output is a substantial determinant of systolic pressure; diastolic pressure is strongly influenced by peripheral vascular resistance.[18] Early after initiation of diuretic therapy, cardiac output has been found reduced and peripheral resistance increased.[14, 15] Neurogenic activity and associated arteriolar vasoconstriction may increase in response to oligemia.[19] After a month of therapy, however, cardiac output is not reduced, and peripheral vascular resistance is decreased;[16] the effect of oligemia is no longer predominant.

Effective blood volume is decreased by drugs that reduce venous return, lower cardiac output, or increase vascular capacity. Ganglion-blocking agents and nitrites are hypotensive, particularly by way of reduced venous return.[20, 21] The response to these agents is increased in the standing position. It is not surprising that their hypotensive effects are exaggerated by the oligemia induced by sodium depletion.

Norepinephrine increases effective blood volume by reducing vascular capacity and increasing venous return.[22] These actions oppose the hemodynamic effects of a modest reduction in plasma volume. Protoveratrine B is hypotensive by a reflex action, the Bezold-

Table 7

Response to Norepinephrine during Administration of a Placebo and after Hydrochlorothiazide Combined with Dextran and Angiotensin II

	Blood pressure, mm. Hg				
	Placebo		Hydrochlorothiazide and Dextran and angiotensin II		
Patient	Before norepinephrine	After norepinephrine	Before norepinephrine	After norepinephrine	Rate of angiotensin II mcg./min.
H.F.	203/112	224/130	198/116	226/122	0.25
I.F.	210/112	252/131	212/113	262/132	0.1
S.G.	183/114	220/124	180/114	206/123	0.1
M.K.	186/110	220/124	187/114	215/125	0.5
I.R.	177/113	210/131	184/115	205/123	0.5
R.R.	197/98	224/112	183/100	216/109	0.25
B.K.	191/98	240/111	210/98	251/111	0.5
F.B.	211/113	255/124	213/111	248/120	0.5
Mean	195/109	231/123	196/110	229/121	0.3
Mean change from placebo period			+1/+1	−2/−2	
Standard deviation			9.6/2.1	8.9/3.7	
p			>.1/>.05	>.1/>.05	

Jarisch effect,[23] which reduces arteriolar tone with or without a decrease in cardiac output. In the present studies the thiazide-induced changes in systolic or diastolic responses to these two substances were not reversed by re-expansion of plasma volume.

Salt in daily doses of 20 Gm. returns body weight, blood pressure, and responses to vasoactive substances essentially to control levels, despite continued administration of a benzothiadiazine. Body potassium is further depleted.[6] These findings oppose the concept that benzothiadiazines have a direct hypotensive action, and indicate that benzothiadiazines are antihypertensive by way of depletion of sodium and not potassium. It is difficult to relate the antihypertensive effects to a correction of excess body salt or water, since total body water, extracellular volume, plasma volume, and 24-hour exchangeable sodium are not greater in patients with uncomplicated essential hypertension than in normotensive subjects.[24]

Changes in extracellular-intracellular sodium gradient can affect contractility.[25] However, the losses of sodium and water associated with the administration of a thiazide were consistent with the loss of isotonic extracellular fluid in studies in another and in this laboratory.[2, 6] Others found intracellular water or sodium depleted.[17, 26]

The present studies suggest that the ability of arterioles to constrict is not impaired by hydrochlorothiazide. It had been considered that if a diuretic reduced arteriolar contractility, the per cent rise in blood pressure during an infusion of norepinephrine would be lower after administration of a diuretic than in a control period. However, the relative increments of response to norepinephrine were not decreased by hydrochlorothiazide. On the other hand, since the basal blood pressure was reduced by the diuretic, the relative increments of response to norepinephrine from this lower level of blood pressure might have been greater if arteriolar contractility had not been impaired. To circumvent the differences in both plasma volume and pre-infusion blood pressure, plasma volume was re-expanded by Dextran, and a continuous intravenous infusion of angiotensin II was added at a rate determined to return the blood pressure to the prediuretic levels. Under these circumstances the response to norepinephrine was similar to that before administration of the diuretic.

Hypertensive and normotensive subjects differ in response to a benzothiadiazine. Chlo-

rothiazide does not reduce the basal blood pressure in normotensive subjects, although it reduces the responses to norepinephrine and increases the response to trimethapan; repletion of the plasma volume in these patients fully restores the norepinephrine and trimethapan responses to prediuretic levels.[27] It appears that compensatory mechanisms normally are adequate to maintain the basal blood pressure despite a mild reduction in plasma volume, and that benzothiadiazines affect the blood pressure responses to pressor and depressor drugs in normotensive subjects only by way of hypovolemia. These observations stand in contrast to the observations in hypertensive patients.

The effects of sodium depletion on the basal blood pressure and the blood pressure responses to vasoactive substances in hypertensive patients can be explained by the hemodynamic effects of oligemia on systolic pressure and by an additional mechanism that decreases peripheral vascular resistance. Since there is indirect evidence that arteriolar contractility is not impaired, the concept is suggested that salt depletion reduces the degree of vasoconstrictor stimulation of the arteriolar bed. A decrease in extracellular volume, a local change in sodium concentration, or a secondary effect of chronic hypovolemia may interfere with a humoral or neurogenic pressor mechanism by which the hypertensive state is maintained. The amounts of angiotensin II necessary to restore the blood pressure to pretreatment levels during thiazide administration were small, averaging 0.3 mcg. per minute. An investigation of the effects of sodium depletion on humoral and neurogenic vasoconstrictor activity is planned.

Summary and Conclusions

Hydrochlorothiazide reduced significantly the basal systolic and diastolic pressures and the levels of blood pressure during infusions of norepinephrine in 10 hypertensive subjects. The diuretic increased the depressor responses to a ganglion-blocking agent, trimethapan, and a nitrite, erythrol tetranitrate. Re-expansion of plasma volume by Dextran lessened the effects of hydrochlorothiazide on basal systolic pressure and systolic responses to trimethapan and erythrol tetranitrate, but did not reverse the effects of the diuretic on basal diastolic pressure, systolic responses to norepinephrine or protoveratrine B, or diastolic responses to the four vasoactive substances studied. Addition of 20 Gm. of salt daily returned all blood pressure responses approximately to control levels.

It is concluded that the antihypertensive effects of hydrochlorothiazide are related to salt depletion, which acts by an effect of oligemia on systolic pressure and by an additional mechanism that decreases peripheral vascular resistance. The induced oligemia plays an important role therapeutically because it exaggerates the hypotensive effects of drugs that reduce venous return or increase vascular capacity.

Two indirect studies suggest that arteriolar contractility is not impaired by the degree of salt depletion induced by hydrochlorothiazide. 1. The relative increments of response to norepinephrine were not decreased by the diuretic. 2. After re-expansion of plasma volume by Dextran and the addition of an intravenous infusion of angiotensin II at a rate determined to return systolic and diastolic pressures to prediuretic levels during continued administration of hydrochlorothiazide, the response to norepinephrine was similar to that before the diuretic was administered.

The combined observations suggest that the antihypertensive effects of salt depletion result from the hemodynamic effects of oligemia and another action which reduces the degree of humoral or neurogenic vasoconstrictor stimulation of the arteriolar bed.

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Effect of Pitressin on the Splanchnic Circulation in Man

By Stanley Shaldon, M.D., Wolfgang Dolle, M.D., Luis Guevara, M.D., Frank L. Iber, M.D., and Sheila Sherlock, M.D.

POSTERIOR PITUITARY EXTRACT is known to lower the portal venous pressure in animals,[1-3] and in man a similar effect has been demonstrated during the control of bleeding from esophageal varices with intravenous pitressin.[4-6] It has been suggested that pitressin lowers portal pressure by increasing splanchnic resistance.[7]

The present communication concerns the effects of intravenous pitressin on splanchnic hemodynamics in control subjects and in patients with liver disease. The patients included some with cirrhosis in whom the portal vein was patent and some with a surgical portacaval anastomosis. Patients with normal liver structure but with occlusion of the portal vein were also studied. It was thus possible to study the effects of pitressin upon the splanchnic hemodynamics as a whole, and also upon the liver hemodynamics independent of the splanchnic bed in patients in whom portal venous blood was totally diverted from the liver.

Methods

The patients were divided into three groups. Group 1 consisted of four subjects without liver disease, group 2 consisted of 10 patients with portal cirrhosis in whom splenic venography had confirmed that the portal vein was patent. These patients had varying degrees of portal hypertension. Group 3 consisted of 11 patients with portal cirrhosis and a patent end-to-side portacaval anastomosis confirmed by splenic venography, and two patients in whom splenic venography showed a blocked portal vein and who had a normal liver biopsy.

Estimation of Hepatic Blood Flow

A size-9 radiopaque cardiac catheter was introduced into one of the main right hepatic veins under fluoroscopic control. The catheter was positioned freely in the central portion of the right lobe of the liver and the exact site of the tip was observed. If the catheter was advanced for a wedged hepatic venous pressure determination, it was subsequently repositioned in the previous "free" sampling position. After an initial priming dose of 20 to 40 mg. of bromsulphalein (BSP), a constant infusion of BSP varying from 1.5 to 4.0 mg. per minute was given intravenously from a Sigma pump attached to a calibrated burette. Paired blood samples for BSP analysis[8] were withdrawn at 10-minute intervals from the hepatic vein catheter and an indwelling needle in a femoral artery. A minimum of three pairs of samples was obtained for estimation of basal hepatic blood flow, which was calculated by Fick principle, with the correction formula for changing arterial levels of BSP when required.[9]

Pressure Determination

The mean arterial pressure (MAP) was calculated from the formula:—

MAP mm. Hg. = diastolic pressure + 1/3 pulse pressure (recorded at 2-minute intervals with a sphygnomanometer).

The wedged hepatic venous pressure (WHVP) was measured by advancing the hepatic vein catheter into the wedged position,[10] the free hepatic venous pressure (FHVP) was recorded after the abrupt drop in pressure in the wedged position when the catheter lay freely in a main hepatic vein.

Serial intrasplenic pressures (ISP) were recorded after percutaneous splenic puncture[11] and the introduction of a polythene catheter into the spleen.[12]

All pressures were recorded with an Elema-Schonander electromanometer with zero reference point situated 5 cm. below the sternal angle. Mean pressure measurements were calculated by planimetry to the nearest 0.5 mm. Hg from electrically damped tracings showing minimal respiratory fluctuations. Pressures were recorded before the start of the BSP infusion and at the end of the basal period, 20 minutes after starting the pitressin infusion and on at least two subsequent occasions in the following 40 minutes, and if the BSP was continued to beyond 60 minutes from starting pitressin on three to four subsequent occasions. In certain patients pressure recordings

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Table 1

Group	Case no.	WHVP 1	WHVP 2	WHVP 3	WHVP %	FHVP 1	FHVP 2	FHVP 3	FHVP %	ISP 1	ISP 2	ISP 3	ISP %	PVP^c 1	PVP^c 2	PVP^c 3	PVP^c %	MAP 1	MAP P	MAP 2	MAP 3	MAP %
		mm. Hg				mm. Hg				mm. Hg				mm. Hg				mm. Hg				
1	1	9.0	5.0	8.0	−44	4.5	3.0	4.5	−33	11.0	6.0	10.5	−45	10.0	5.5	10.5	−45	95	120	95	90	+26
	2	11.0	6.5		−41	4.5	3.0		−33	13.0	7.5		−42	12.0	7.0		−42	85	115	85		+35
	3	7.5	5.0		−33	4.5	3.0		−33									95	115	95		+31
	4	12.0	7.0		−42	5.0	3.0		−40									100	130	95		+30
2	5	23.0	14.5		−37	5.0	4.0		−20									110	135	110		+23
	6	14.5	6.5		−54	6.0	3.0		−50	18.0	9.5		−47	16.0	8.0		−50	95	115	90		+31
	7	22.0	14.0	21.0	−36	6.0	4.0	6.0	−33	28.0	18.0	26.0	−36	25.0	16.0	23.0	−36	100	125	100	100	+25
	8	26.0	13.0	25.0	−50	6.0	4.0	6.0	−33									105	115	105	105	+ 9
	9	25.0	13.5		−46	10.0	6.0		−40									90	105	90		+28
	10									30.0	15.0		−50					85	95	85		+12
	11									28.0	14.0		−50					80	95	85		+19
	12									30.0	18.0		−40					90	110	90		+26
	13									31.0	17.0		−45					90	100	90		+11
	14									21.0	12.0		−42					85	95	90		+12
3	15	20.0	14.0		−30	9.0	7.5		−17	16.5	11.5		−30					100	115	100		+13
	16	18.0	12.0	16.5	−33	6.0	4.5	5.5	−25	14.0	8.0	13.0	−43					90	105	90	90	+16
	17	18.0	10.0		−45	5.0	3.0		−40	11.0	7.0		−36					85	95	85		+12
	18	15.0	8.5		−42	6.5	3.5		−46									85	95	85		+12
	19	13.5	10.0	14.0	−26	4.5	4.0	5.0	−11	11.5	7.0		−41					95	100	95		+ 6
	20									13.5	10.0	14.0	−26					80	90	80	80	+12
	21	9.5	6.0		−37	3.0	1.5		−50									85	100	85		+18
	22	24.5	14.5		−41	10.0	5.0		−50	8.5	5.0		−35					80	95	80		+15
	23	12.0	7.5		−37	6.5	5.0		−23	8.0	4.5		−44					80	95	80		+15
	24									12.0	6.0	12.5	−50					85	100	85	85	+17
	25	11.5	8.0		−30	5.0	4.0		−20	13.5	9.0		−33					95	110	95		+16
	26*	6.5	4.0		−38	2.0	1.5		−25	22.0	9.0		−59					100	120	100		+20
	27*	4.5	3.0		−33	2.5	1.5		−40	28.0	16.0		−43					75	85	75		+13
	Nos.				20				20				20				4					27
	Means of percentage change				−38.7				−33.1				−41.9				−43.3					+18.7
	S.D.				7.2				11.6				7.3									7.8
	28†	15.5	13.0	15.5	−16	6.5	5.5	6.5	−15									90	110	90	90	+22

*Patients with thrombosed portal vein and normal livers.

†Case no. 28, patient with cirrhosis in group 2, received only 10 units of pitressin.

1 = Period 1—20 minutes prior to pitressin administration. 2 = Period 2—40 minutes' duration commencing 20 minutes after start of pitressin infusion. 3 = Period 3—30 to 40 minutes duration following Period 2. P = time during pitressin infusion—10 minutes. % changes refer to maximal changes seen in Period 2 compared with Period 1, except for mean arterial pressure, where maximal change was seen during pitressin infusion period (P).

were made without hepatic blood flow determinations, and occasionally only the wedged hepatic venous or intrasplenic pressures were measured. If both pressure measurements were determined in patients with a patent portal vein, the calculated portal venous pressure (PVP^c) was derived from the formula:

$$\text{PVP}^c \text{ mm. Hg} = \frac{\text{ISP} + \text{WHVP}}{2}$$

Resistances

Resistances were calculated from a modification of Poiseuille's law.[13]

$$\frac{\text{Pressure gradient mm. Hg} \times 80}{\text{Blood flow L. per minute}} = \text{Resistance (dynes sec. cm.}^{-5})$$

Postsinusoidal resistance (PSR) defined as the resistance to hepatic venous outflow was calculated from the formula:

$$\text{PSR dynes sec. cm.}^{-5} = \frac{\text{WHVP} - \text{FHVP} \times 80}{\text{EHBF L. per min.}}$$

EHBF = estimated hepatic blood flow.

Splanchnic resistance (SR) defined as the arteriolar resistance to inflow of blood to the splanchnic

Effects of Pitressin on Splanchnic Hemodynamics in All Groups

EHBF				PSR				SR				HAR			
1	2	3	%	1	2	3	%	1	2	3	%	1	2	3	%
ml. per min.								dynes seconds cm.$^{-5}$							
1,320	700	990	−47	250	230	320	− 9	5,100	10,200	6,900	+100				
1,410	790		−44	370	360		− 3	4,400	8,300		+ 85				
1,590	850		−46	150	190		+26	4,300	8,500		+ 97				
1,180	700		−41	1,200	1,200		− 2	5,900	19,800		+ 83				
1,030	680	1,020	−34	1,240	1,180	1,180	− 5	5,800	9,800	6,000	+ 68				
710	400		−44	1,240	1,300		+ 5					9,060	17,300		+ 92
810	520	710	−37	1,180	1,170	1,240	0					7,100	12,100	8,300	+ 71
1,110	590		−47	940	950		0					4,800	10,200		+110
580	370		−36	1,180	1,030		−15					9,600	10,500		+ 72
550	400		−27	950	900		− 5					11,000	15,800		+ 44
670	420		−37	1,730	1,810		+ 5					6,500	12,500		+ 92
1,240	710		−43	290	280		− 3					6,100	10,800		+ 77
500	320		−36	320	370		+16					11,200	18,100		+ 62
			13				13				5				8
			−39.9				+0.76				+86.6				+77.5
			6.1				10.6				12.8				20.4
610	500	580	−18	1,180	1,250	1,240	+ 7	11,000	13,900	10,500	+26				

WHVP = wedge hepatic venous pressure. FHVP = free hepatic venous pressure. ISP = intrasplenic pressure. PVP^{c} = calculated portal venous pressure. MAP = mean arterial pressure. EHBF = estimated hepatic blood flow (BSP). PSR = postsinusoidal resistance. SR = splanchnic resistance. HAR = hepatic arteriolar resistance.

bed including the liver was calculated for all patients with a patent portal vein from the formula:

$$\text{SR dynes sec. cm.}^{-5} = \frac{\text{MAP—PVP}^{c} \times 80}{\text{EHBF L. per min.}}$$

In some patients with a patent portal vein (groups 1 and 2) the intrasplenic pressure was not measured, and consequently the splanchnic resistance was calculated from the MAP-WHVP pressure gradient. Hepatic arteriolar resistance (HAR) defined as the resistance to the inflow of blood to the liver via the hepatic artery alone, in patients in whom portal venous blood was totally diverted from the liver (group 3) was calculated from the formula:

$$\text{HAR dynes sec. cm.}^{-5} = \frac{\text{MAP—WHVP} \times 80}{\text{EHBF L. per. min.}}$$

Procedure

Twenty units of pitressin (Parke-Davis) (diluted in 100 ml. of 5 per cent dextrose) were infused intravenously over a 10-minute period. During the pitressin infusion and for a further 10 minutes after completion of the infusion, (0 to 20 minutes), no samples of blood were taken. After this time interval further paired samples of arterial and hepatic venous blood were obtained for BSP analysis at 10-minute intervals up to 60 minutes following the commencement of the pitressin infusion (20 to 60 minutes). In certain patients the sampling was extended to 100 minutes after

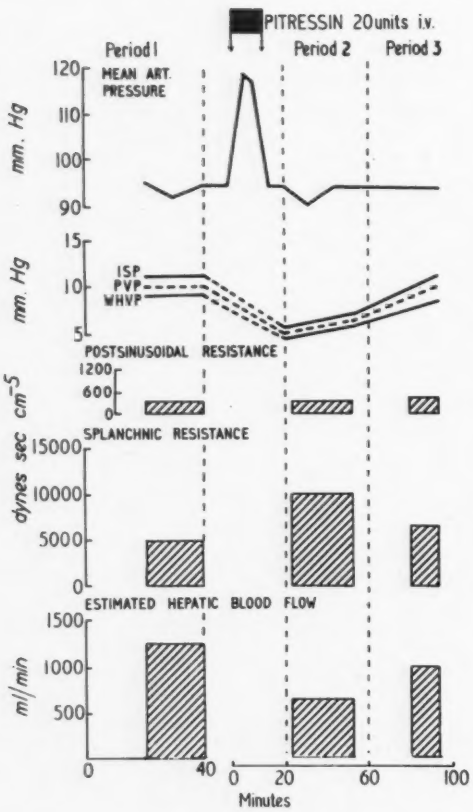

Figure 1

The effect of 20 units of pitressin on the splanchnic hemodynamics—control subject (no. 1) (group 1). The portal pressure was reduced by 45 per cent and the estimated hepatic blood flow fell by 47 per cent, while the splanchnic resistance increased by 100 per cent during period 2. The postsinusoidal resistance was unchanged. All parameters had almost returned to baseline levels during period 3. ISP = intrasplenic pressure; PVP = calculated portal venous pressure; WHVP = wedged hepatic venous pressure.

the start of the pitressin infusion. In one patient with cirrhosis and a patent portal vein (no. 28) only 10 units of pitressin were infused. Preliminary electrocardiographic tracings were taken in all cases, and pitressin was not given to any patient with electrocardiographic evidence of myocardial ischemia.

Results

The results are tabulated (table 1) as mean hepatic blood flow determinations, pressures, and calculated resistances for the following time periods:

Period 1 = control period before pitressin infusion.

Period 2 = 20 to 60 minutes after commencing the pitressin infusion. [Only the mean arterial pressure was recorded during the pitressin infusion (0 to 10 minutes) and for the subsequent 10 minutes]

Period 3 = 60 to 100 minutes after commencing the pitressin infusion.

The results are expressed in absolute values and also as the percentage alteration of the parameters in period 2 as compared with period 1 except for the mean arterial pressure where the maximal increase (P) occurred during the pitressin infusion, and this increase is also expressed as a percentage of the baseline mean arterial pressure. Statistical analyses[14] are confined to the percentage changes because the absolute variations among the groups are too large to permit a valid statistical assessment of the absolute measurements.

Patients without liver disease (Group 1). In four control subjects the wedged hepatic venous pressure was reduced by an average of 4.5 mm. Hg during period 2. The percentage reduction averaged 40 per cent. The free hepatic venous pressure was reduced by an average of 35 per cent. In two of these patients the intrasplenic pressure fell by 5.5 mm. Hg representing a 45 and 47 per cent reduction and the calculated portal venous pressure fell by a similar amount. The maximum increase in mean arterial pressure occurred during the pitressin infusion and averaged 30 per cent but the systemic blood pressure had returned to baseline levels in all cases before period 2. In three control patients estimated hepatic blood flow was reduced by an average of 660 ml. per min. representing a reduction of 45 per cent. The calculated splanchnic resistance averaged 4,450 dynes seconds cm.$^{-5}$ in these three patients, and was increased by an average of 94 per cent during period 2. The postsinusoidal resistance averaged 260 dynes cm.$^{-5}$ and was not consistently altered following the pitressin infusion (two subjects showed

a slight reduction of 2 and 9 per cent and one subject showed an increase of 26 per cent). In one subject (no. 1, fig. 1) these measurements were extended to period 3 and all parameters had almost returned to baseline levels 80 minutes after commencing the pitressin.

Patients with portal cirrhosis and a patent portal vein (Group 2). In five patients the wedged hepatic venous pressure fell by an average of 10 mm. Hg representing a 36 to 54 per cent reduction during period 2. The free hepatic venous pressure was reduced by an average of 35 per cent. In seven patients (including two in whom the wedged hepatic venous pressures were measured simultaneously) the mean reduction in intrasplenic pressure was 43 per cent representing an absolute pressure reduction of 11.6 mm. Hg. The calculated portal venous pressure in two patients was reduced by 36 and 50 per cent during period 2. The maximum increase in mean arterial pressure occurred during the pitressin infusion and averaged 24 per cent, but had returned to baseline levels in all cases before period 2. In two patients estimated hepatic blood flow was reduced by 41 and 34 per cent respectively, representing an absolute reduction of 480 and 340 ml. per minute during period 2. The calculated splanchnic resistances during the control period in these two patients were 5,900 and 5,800 dynes seconds cm.$^{-5}$ and there was an 83 and 68 per cent increase in these resistances during period 2. The postsinusoidal resistances during the control period were 1,200 and 1,240 dynes second cm.$^{-5}$ and were virtually unaffected by the pitressin infusion. In one patient (no. 7, fig. 2) measurements were extended to period 3 and all parameters had returned to baseline levels by 80 minutes after starting the pitressin infusion.

In one patient (no. 28) 10 units of pitressin produced a 15 per cent reduction in wedged and free hepatic venous pressures, an 18 per cent reduction in estimated hepatic blood flow, and a 26 per cent increase in splanchnic resistance during period 2. The postsinusoidal resistance was not significantly altered, the effects lasted for a similar period of time to the 20-unit pitressin infusion.

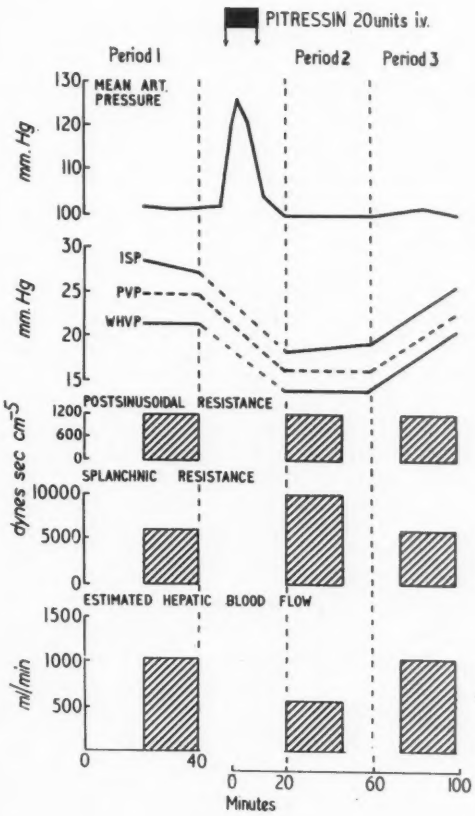

Figure 2

The effect of 20 units of pitressin on the splanchnic hemodynamics—cirrhotic patient (no. 7), with a patent portal vein (group 2). The portal pressure was reduced by 36 per cent and the estimated hepatic blood flow fell by 34 per cent, while the splanchnic resistance increased by 68 per cent during period 2. The postsinusoidal resistance was not affected. Parameters were returning to baseline levels during period 3. ISP = intrasplenic pressure; PVP = calculated portal venous pressure; WHVP = wedged hepatic venous pressure.

Patients with total diversion of portal blood from the liver (Group 3).

Patients with portal cirrhosis and a patent portacaval anastomosis. In nine patients the wedged hepatic venous pressure was reduced by an average of 5.6 mm. Hg during period 2. The percentage reduction averaged 36 per cent; the free hepatic venous pressure was reduced by an average of 31 per cent. In nine

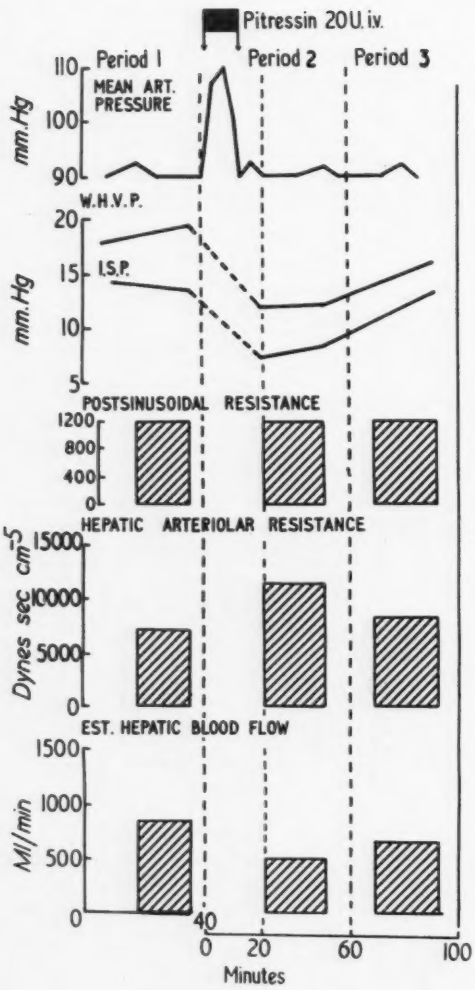

Figure 3

The effect of 20 units of pitressin on the splanchnic hemodynamics—cirrhotic patient (no. 22) with an end-to-side portacaval anastomosis (group 3). Estimated hepatic blood flow was reduced by 37 per cent and the wedged hepatic venous pressure fell by 43 per cent. Hepatic arteriolar resistance was increased by 71 per cent and the postsinusoidal resistance was not altered during period 2. The intrasplenic pressure was reduced by 43 per cent during period 2. All parameters were returning to baseline during period 3.

patients (including seven in whom the wedged hepatic venous pressure was measured simultaneously) the intrasplenic pressure fell by an average of 38 per cent, representing an obsolute reduction of 4.5 mm. Hg. The maximum increase in mean arterial pressure occurred during the pitressin infusion and averaged 14 per cent. Arterial pressures had returned to baseline levels in all patients by the start of period 2. In six patients the estimated hepatic blood flow fell by an average of 38 per cent. The absolute reduction in flow averaged 290 ml. per minute.

The hepatic arteriolar resistance in six patients averaged 8,000 dynes seconds cm.$^{-5}$ during the control period and was increased by an average of 60 per cent during period 2. The postsinusoidal resistance averaged 1,200 dynes seconds cm.$^{-5}$ in the control period and was not consistently altered following the pitressin infusion (two patients showed no change, two patients showed a reduction of 5 and 15 per cent, and two patients had an increase of 5 per cent in postsinusoidal resistance). In one patient (no. 22, fig. 3) measurements were extended to period 3 and all parameters had almost returned to baseline about minutes after the start of the pitressin infusion.

Patients with portal venous thrombosis and a normal liver. In two patients the wedged hepatic venous pressures fell by 38 and 33 per cent respectively. The free hepatic venous pressures were reduced by 25 and 40 per cent (fig. 4). The simultaneously determined intrasplenic pressures fell by 59 and 43 per cent, representing an absolute reduction of 13 and 12 mm. Hg. The maximum increases in arterial pressures were seen during the pitressin infusion and were 20 and 13 per cent respectively. Estimated hepatic blood flows were reduced by 43 and 36 per cent. The hepatic arteriolar resistances in the control period in these two patients were 6,100 and 11,200 dynes sec. cm.$^{-5}$ respectively and were increased by 77 and 62 per cent during period 2. The postsinusoidal resistances were 290 and 320 dynes seconds cm.$^{-5}$ in the control period and were not significantly altered during period 2.

Combined Results for All Groups

The mean percentage alterations during period 2 following 20 units of pitressin for

the various parameters for all groups were determined. The wedged hepatic venous pressure was reduced by 38.7* ± 7.2 per cent, the free hepatic venous pressure was reduced by 33.1 ± 11.6 per cent, and the intrasplenic pressure was reduced by 41.9 ± 7.7 per cent for 20 patients. The estimated hepatic blood flow was reduced by 39.9 ± 6.1 per cent in 13 patients. The postsinusoidal resistance was increased by 0.76 per cent, which was not significantly different from zero ($0.8 < p < 0.9$). The splanchnic resistance in five patients with a patent portal vein (groups 1 and 2) increased by 86.6 ± 12.7 per cent. The hepatic arteriolar resistance in eight patients with a total diversion of portal blood flow to the liver (group 3) was increased by 77.5 ± 20.4 per cent. There was no significant difference between the mean increase in splanchnic resistance in control and cirrhotic patients or the mean increase in hepatic arteriolar resistance in patients with cirrhotic or normal livers and total diversion of portal venous blood. Similarly there was no significant difference between the groups in the percentage changes in parameters induced by pitressin except for the smaller increase in mean arterial pressures seen in group 3. The percentage changes were all in the same direction in the patient who received 10 units of pitressin but were lower than the 95 per cent lower limits of the changes induced by 20 units of pitressin.

Side Effects

Most patients experienced abdominal discomfort with cramp sensations and evacuation of the bowels during the pitressin infusion and also tightness of the skin with marked facial pallor. These side effects passed off rapidly and were not present during the measurements made in periods 2 and 3.

Discussion

The validity of the calculation of resistance in the splanchnic circulation is dependent upon several assumptions. The abrupt drop in pressure seen on withdrawing a catheter from the wedged hepatic position suggests that the site of resistance to hepatic venous outflow is located at the site of pressure drop. The wedged hepatic venous pressure is almost certainly a measure of hepatic sinusoidal pressure[15] and its close agreement with the directly recorded portal venous pressure[10, 15–17] depends upon the free flow of portal blood from the portal vein to the hepatic sinusoids, through a low-resistance circuit. In the presence of obstruction to portal venous flow or surgical diversion of portal blood through a portacaval anastomosis, the wedged hepatic venous pressure is no longer related to the portal pressure[16, 18] and reflects only the hepatic sinusoidal pressure. Hence the site of resistance to hepatic venous outflow may be located anywhere between the sinusoids and the main hepatic veins. The anatomic location of this resistance does not detract from the validity of calculating the resistance from the pressure gradient and the estimated hepatic blood flow. The gradient between the free hepatic vein pressure and the inferior vena caval pressure rarely exceeds 1 mm. Hg and so adds little to the postsinusoidal resistance. The calculation of splanchnic resistance is dependent upon the assumption that estimated hepatic blood flow equals splanchnic blood flow, and that the measured indirect portal pressure corresponds to the pressure on the venous side of the mesenteric vessels. In the absence of a portal collateral circulation, hepatic blood flow must equal splanchnic blood flow. If a portal collateral circulation exists as in the two patients in group 2, the calculated splanchnic resistance is overestimated. Nevertheless, the percentage changes induced by pitressin are probably valid measures of the changes in splanchnic resistance even if the absolute measurements are overestimated. In order to determine the best estimate of portal venous pressure, a mean of the intrasplenic and wedged hepatic venous pressures was used if both were available and the portal vein was unobstructed and in functional continuity with the liver.

The concept of hepatic arteriolar resistance was introduced to estimate the resistance to inflow of hepatic arterial blood to the liver in patients in whom portal venous blood was totally diverted from the liver. If the wedged

*± = One standard deviation.

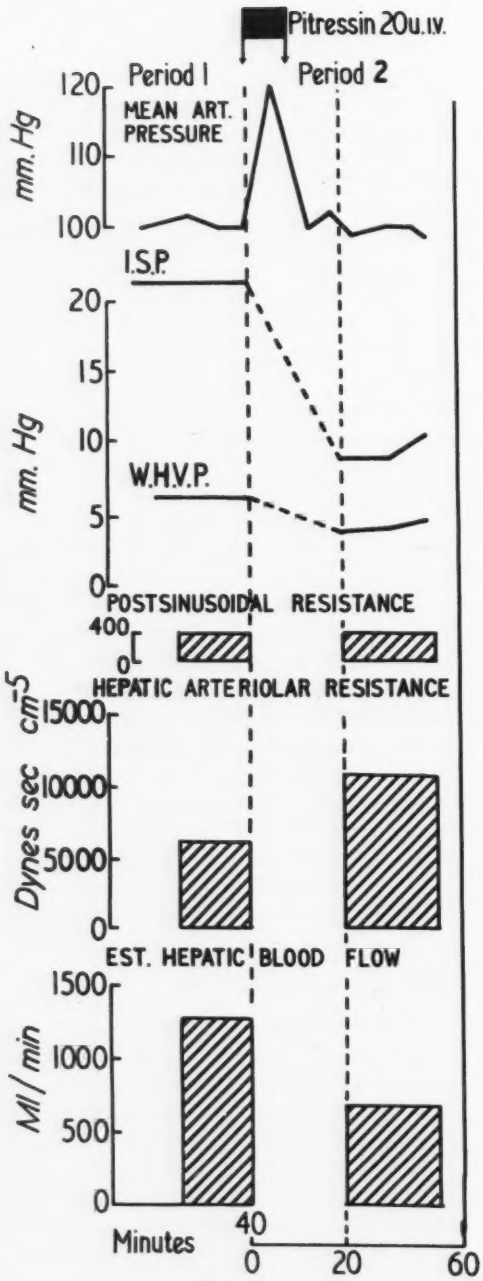

Figure 4

The effect of 20 units of pitressin on the splanchnic hemodynamics—patient (no. 26) with a portal vein thrombosis and a normal liver (group 3). Estimated hepatic blood flow was reduced by 41 per cent and the wedged hepatic venous pressure fell by 38 per cent. Hepatic arteriolar resistance was increased by 77 per cent, while the postsinusoidal resistance was not affected during period 2. The intrasplenic pressure was reduced by 59 per cent during period 2.

hepatic venous pressure measures hepatic sinusoidal pressure, then this calculated resistance is valid. In these patients the mesenteric component of the splanchnic resistance could not be calculated as the blood flow in the portal vein was not measured, but the pressure in the portal circuit was measured by splenic pressure recordings and changes in this pressure were interpreted as indexing changes in mesenteric arteriolar resistance.

The mechanism whereby pitressin lowers the portal pressure is related to the increase in calculated splanchnic resistance in patients with an intact portal vein. In patients with total prehepatic deviation of portal blood the reduction in portal pressure (ISP) was of a similar degree to that observed in patients with a patent portal vein and suggests therefore that the mesenteric arteriolar resistance was increased as well as the hepatic arteriolar resistance in these patients. The similarity of response in patients with and without cirrhosis, suggests that pitressin affects the mesenteric arterioles of the cirrhotic and noncirrhotic patient to a similar degree. It is therefore unlikely that functional arterial venous anastomoses in the mesentery are operative in the pathogenesis of portal hypertension in cirrhosis as has been suggested by Leevy and Gliedman.[19] A vasoconstrictor agent would have a smaller effect on an arteriovenous anastomosis than upon an arteriolar capillary venous circuit.

In patients with total prehepatic deviation of portal blood, pitressin reduced the hepatic blood flow by an increase in the hepatic arteriolar resistance. There was no significant difference in the basal hepatic arteriolar resistances of the cirrhotic and noncirrhotic patients with no portal blood flowing to the liver (group 3), or in the per cent increase in hepatic arteriolar resistance following the pitressin infusion. This latter observation suggests that hepatic arteriolar sinusoidal anas-

tomoses are consequently unlikely to be operative in the genesis of portal hypertension in patients with cirrhosis.

The reduction in hepatic arterial blood flow in patients with cirrhosis is undesirable, as morphologic evidence suggests that regeneration nodules derive their blood supply entirely from the hepatic artery.[20] The repeated use of pitressin in clinical trials in the control of bleeding varices did not result in hepatic ischemia.[6] Furthermore Davis and co-workers [21] have shown that hepatic oxygen consumption is not reduced when hepatic blood flow is reduced by pitressin. The action of the intravenously administered pitressin on the splanchnic circulation did not exceed 1 hour and, as a therapeutic measure, this is obviously disadvantageous. The peripheral vasoconstrictor effect was even more transient, as the mean arterial pressure was elevated only during the pitressin infusion of 10 minutes' duration.

The over-all circulatory effect of pitressin appears to be a redistribution of blood flow in the body, as the cardiac output is not altered.[21] The reported increase in skeletal muscle blood flow[22] probably accounts therefore for the reduction in the skin,[22] renal,[21] and splanchnic blood flow. The hepatic venous blood outflow resistance (postsinusoidal resistance) was not altered, and this resistance may not be subject to vasoconstrictor effects in man.

In patients with cirrhosis the postsinusoidal resistance was raised above the control range of 244 ± 78 dynes seconds cm.$^{-5}$ established in this laboratory. The postsinusoidal resistance in cirrhosis may not be significantly reduced by a portacaval anastomosis, as all patients with cirrhosis and a portacaval anastomosis in group 3 had an elevated postsinusoidal resistance, and previous work[18] showed no significant alteration in postsinusoidal resistance calculated in absolute units in 10 patients with cirrhosis before and after a portacaval anastomosis. The elevation of the postsinusoidal resistance in cirrhosis conrms morphologic opinions[20, 23, 24] that the fundamental lesion responsible for portal hypertension in cirrhosis is an obstruction to hepatic venous outflow by constriction of the hepatic veins with regeneration nodules. The normal postsinusoidal resistance in patients with an extrahepatic portal venous obstruction and a normal liver structure clearly demonstrated that portal hypertension in these cases is not related to intrinsic liver disease. If the postsinusoidal resistance is maintained by an organic reduction of the hepatic venous outflow tract, it is unlikely that drugs will affect this resistance. Previous workers[25-28] have reported changes in hepatic blood flow or portal pressure under a variety of circumstances, and in all these conditions changes in the splanchnic resistance were implicated.

The elevated postsinusoidal resistance in cirrhosis is probably only reduced with prolonged medical treatment and diuretic therapy in patients with ascites or fatty livers.[29] In these patients one may postulate a reduction in intrahepatic edema or fat as the mechanism whereby the hepatic venous outflow obstruction is reduced. One may therefore conclude that pharmacologically induced reductions in the portal pressure may only be achieved by increasing the splanchnic resistance, and pitressin is the most potent splanchnic vasoconstrictor available.

Summary

The effects of 20 units of pitressin administered intravenously on the splanchnic circulation in four patients without liver disease, 10 patients with cirrhosis and a patent portal vein, 11 patients with cirrhosis and an end-to-side portacaval anastomosis and two patients with an extrahepatic portal vein obstruction and a normal liver structure, were observed. Estimated hepatic blood flow and wedged hepatic venous and intrasplenic pressures were measured in all groups, and the splanchnic, hepatic arteriolar, and hepatic postsinusoidal resistances were calculated. Pitressin reduced the portal pressure by an average of 39 per cent for 1 hour. Estimated hepatic blood flow was reduced by 40 per cent. Splanchnic resistance was increased by 87 per cent and hepatic arteriolar resistance by 77 per cent. Postsinusoidal resistance was not affected. The drop in portal pressure could be

related to the increases in splanchnic resistance. There was no difference in the response to pitressin between patients with cirrhosis and patients with normal liver structure and function. It is suggested that the fundamental lesion causing portal hypertension in cirrhosis is an obstruction to the hepatic venous outflow and that mesenteric and hepatic arteriolar venous anastomoses are not operative in the genesis of portal hypertension in cirrhosis. This obstruction to hepatic venous outflow is not alterable pharmacologically and any attempts to lower portal pressure by medical means must be achieved by alterations in the splanchnic resistance. Pitressin appears to be the most potent splanchnic vasoconstrictor available.

Acknowledgment

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Biological thought has never attained to that finality which appears, at least by contrast, to characterize the greater body of opinions in physical science.

In particular two extreme views, though often commingled, have continually striven for the mastery. The one of these, purely scientific and wholly positive, declares the phenomena of life to be, while partly unknown, ultimately knowable as manifestations of matter and energy. According to this view life is a mechanism and nothing more, in its positive scientific aspects at least. Without necessarily denying such assertions, the other view sees the unique properties of life to be dependent upon an equally unique force or tendency, operating in or through its physico-chemical organization. Either there is a peculiar vital force; or there is manifest in the organism a peculiar tendency; or at any rate life patently follows the path into which it was propelled by an original impetus, peculiar to life, unknown in other phenomena. All such views inherently partake of metaphysics, and have, therefore, ever aroused most determined opposition among the more orthodox devotees of science.—LAWRENCE J. HENDERSON. *The Fitness of the Environment*. New York, The Macmillan Co., 1924, p. 282.

A Clinical Appraisal of the Vectorcardiogram in Myocardial Infarction

I. The Cube System

By PAUL G. HUGENHOLTZ, M.D., GERALD H. WHIPPLE, M.D., AND HAROLD D. LEVINE, M.D.

IT HAS BEEN ARGUED that the vectorcardiogram should yield no more information than a standard 12-lead electrocardiogram. Yet many authors, including Wolff,[1, 2] Burch,[3-5] Scherlis and Grishman[6] and Milnor,[7] employing different lead systems, have published data indicating that the vectorcardiogram may demonstrate abnormalities not apparent in the electrocardiogram.

Of a total of 2,545 vectorcardiograms recorded over a 2-year period in patients hospitalized at the Peter Bent Brigham Hospital 368 fulfilled the criteria, to be described below, for the diagnosis of myocardial infarction. Sixty-seven of these patients were subsequently examined post mortem. The 368 recordings fell into two groups, one in which the Grishman cube[8] (161 cases) was employed, the other in which the corrected lead system of Frank[9] (207 cases) was used. This communication will deal exclusively with the results obtained by the former technic. Based upon the results of a correlation between anatomic and vectorcardiographic findings, a division into distinct groups of vectorcardiographic patterns was established and these were expressed in numerical values. In addition an evaluation was made of the accuracy of the vectorcardiogram recorded by the cube technic as compared with the standard 12-lead electrocardiogram.

It has been stated that the older vectorcardiographic technics including the Grishman cube, are subject to distorting influences similar to those that affect the 12-lead electrocardiogram. These include variations in body build and dipole position resulting in differences in magnitude and direction of the effective lead axes from patient to patient.[10, 11] Consequently a statistical analysis similar to that applied to the results obtained with the Frank system[9] could not be carried out. Despite these disadvantages of the cube system this material is presented because of the availability of this series of autopsied cases and the continued use of this system in many laboratories.

The modern concepts of vectorcardiography depend upon the visualization of the process of depolarization of the heart as a spatial phenomenon. Although the results of this study would most accurately have been expressed in a mathematical formulation involving spatial coordinates or spatial models they are, we think, most practically communicated to and comprehended by the non-mathematical reader when expressed as the projection of these spatial forces upon two or three mutually perpendicular planes. An abnormal spatial vector may be best appreciated in its projection in an abnormal direction upon a particular plane; however, at the same time, the direction of this abnormal spatial vector may be projected upon another plane as if it still were within normal limits. Conse-

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Studies carried out during tenure of fellowships from Massachusetts Heart Association (Nos. 125 and 290) and the U. S. Public Health Service (HF 8886, H-4284) and with help of Cardiac Research Fund (No. 9264) Peter Bent Brigham Hospital.

quently the abnormality in its projection upon one or two planes would suffice to characterize it as abnormal in space. In these studies the magnitude of vectors was not measured. Accordingly wherever the word "vector" is used without qualification, it indicates its direction only.

Methods and Materials

All of the autopsy material in this study was analyzed in the Department of Pathology and reviewed by a senior pathologist. Routine transverse sections were made through the heart ("bread loafing") and the gross areas of fibrosis and infarction carefully mapped. In addition, a detailed drawing of the state of the coronary system was prepared. Microscopic sections were made of the heart muscle at these sites. No injection studies were done.

The majority of the postmortem examinations were performed within 2 weeks of the recording of the vectorcardiogram and the electrocardiogram. In about half of the remaining cases the interval varied from 1 to 2 months. The remainder were included in the tabulations only if there was no clinical evidence for subsequent infarction.

The material of this study fell into three categories:

Group A: Forty-three individuals, who were eventually examined post mortem. In these the diagnosis of myocardial infarction was *indubitable*.

Group B: Seventy-three patients (not autopsied) in whom the existence of myocardial infarction may be regarded as *probable*. These individuals gave a classical history of severe substernal constricting pain lasting 1 hour or more and demonstrated at least one of the following:

I. The development of significant elevation of the RS-T segment which subsequently subsided entirely.

II. The development of abnormal Q waves in patients not previously exhibiting them. Depending upon the topography of the infarct, the following electrocardiographic criteria had to be met:

1. In the instance of *anteroseptal infarction*, QS complexes in leads V_1, V_2, and V_3 or QS complexes in leads V_1 and V_2 and qR or QR complexes in lead V_3, in the absence of left ventricular hypertrophy or left bundle-branch block.

2. *In anterolateral infarction*, QR complexes in leads V_5 and V_6 provided that the Q waves in these leads measured at least 0.03 second in duration.

3. *In high lateral wall infarction*, Q waves in leads I and aV_L, measuring at least 0.03 second in duration, confirmed by the presence of broad Q waves followed by R waves in high lateral leads.

4. *In apical or diaphragmatic infarction*, Q waves in leads III and aV_F measuring more than 0.04 second in duration and with a depth of more than 25 per cent of the amplitude of the R wave in the same lead.

5. It is to be emphasized that there are no clear-cut criteria in the contemporary literature for

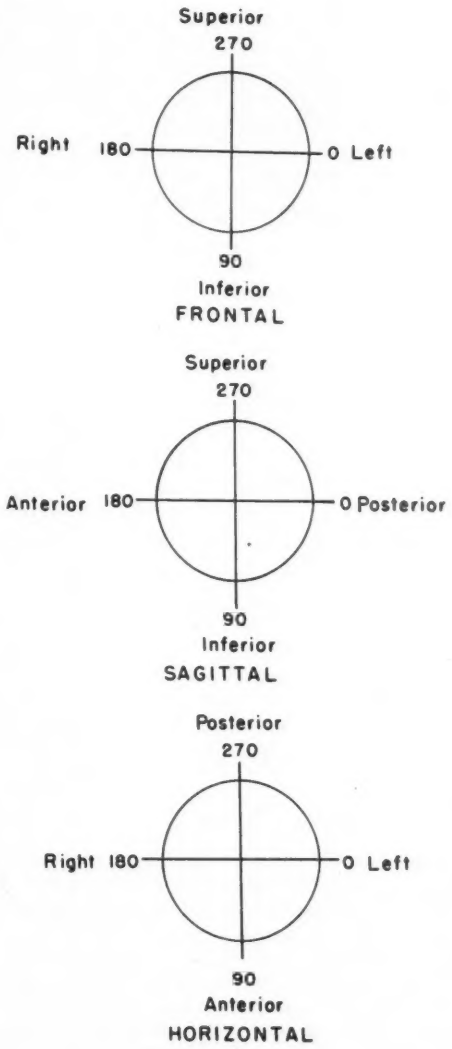

Figure 1

Angular reference frame for presentation of data in three orthogonal planes. Helm's system of notation.[13]

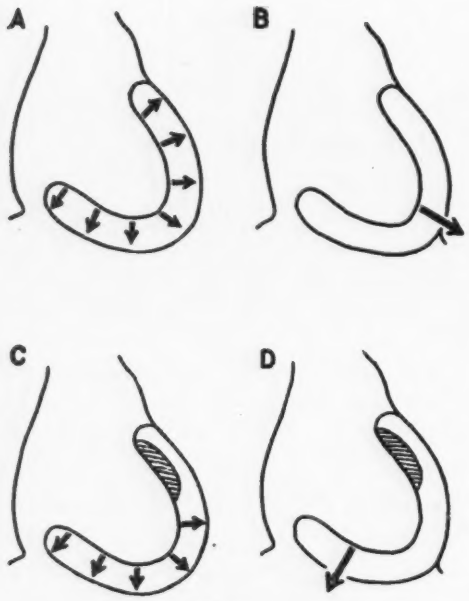

Figure 2

Genesis of abnormality in initial vector in myocardial infarction: A. *Arrows indicate multiple vectors at about 0.03 second.* B. *Resultant normal vector at 0.03 second.* C. *Situation when several vectors are absent as consequence of anterolateral wall infarction.* D. *Deviation of resultant vector ("infarct vector"). (Reproduced from Grant[18] with permission of the author.)*

the diagnosis of *posterobasal* (true posterior, not diaphragmatic) *infarction.*

Q waves in leads III and aV_F measuring between 0.03 and 0.04 second in duration or Q waves in those leads measuring from 10 to 24 per cent of the amplitude of the R wave in the same lead, were considered *questionable* evidence for inferior infarction. In the absence of evidence for left ventricular hypertrophy or left bundle-branch block, a decreasing amplitude of the R wave, or a failure of the R wave to exhibit a normal progressive increase in amplitude as the electrode was moved from right to left over the right precordium, was regarded as *questionable* evidence for anteroseptal infarction.

III. A rise of the lactic acid dehydrogenase level in the blood serum in the absence of other known causes of elevated lactic acid dehydrogenase.[12] This was considered significant either as an isolated reading above 200 units or as a series of observations with a dynamic rise of the lactic acid dehydrogenase level to above the normal

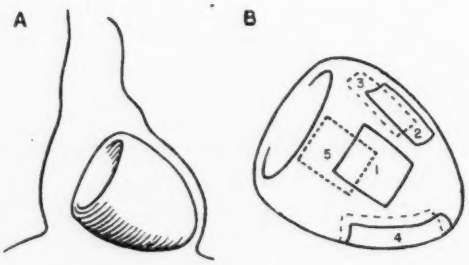

Figure 3

Topography of myocardial infarction. Modified after Grant[18] and reproduced with the permission of the author. Here area 1 represents an anteroseptal infarct; 2, an anterolateral infarct; 3, a high lateral infarct; 4, a diaphragmatic or apical infarct; and 5, a posterobasal or true posterior infarct.

value of 140 units or as a progressive fall from above to below that value.[12] (The presence of an elevated white blood cell count and erythrocyte sedimentation rate was considered confirmatory evidence but was not required.)

Group C. A group of 45 patients in whom the diagnosis was strongly suspected on clinical grounds and in which the vectorcardiogram presented characteristic evidence of myocardial infarction but in which the criteria under group B could not be satisfied. In this group the diagnosis was regarded as *presumptive.*

In groups A (definite infarction) and B (probable infarction) a comparison was made between the interpretation of the standard electrocardiogram and the vectorcardiogram, each recorded on the same day. Cases in group C (possible infarction) were not included in this analysis but the findings in this group were utilized to amplify or to supplement certain observations and conclusions regarding the vectorcardiographic diagnosis of myocardial infarction made in groups A and B.

In all cases the routine 12 leads were recorded with a Sanborn direct-writing electrocardiograph. Leads V_{4R} and V_{3R} were included in all instances. The technic of vectorcardiographic registration was that devised by Grishman and Scherlis.[8] The system is so wired that the sagittal plane is oriented as if the examiner were looking at it from the patient's left side[13, 14] and the horizontal plane as if it were being viewed from above and from in front. Thus in the reproductions of the normal sagittal plane loop it rotates in a counterclockwise direction anteriorly, subsequently inferiorly, and finally posteriorly, then returns to the null-point.

The recording apparatus consisted of two Tektronix preamplifiers and a Dumont oscilloscope

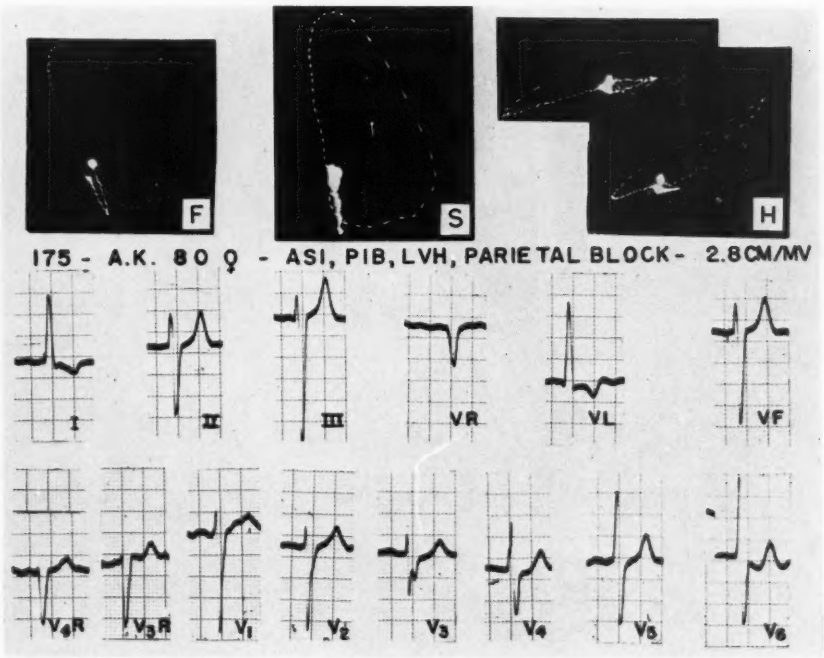

Figure 4

Discrepancy between electrocardiogram and vectorcardiogram. An 80-year-old woman in whom the electrocardiogram showed no evidence for myocardial infarction but in whom the horizontal-plane vectorcardiogram showed the 0.01-second vector at 360°, the 0.02-second vector at 347°, decisive evidence for anteroseptal infarct. This was confirmed at postmortem examination. PIB, peri-infarction block.[18]

mounted on a portable unit so that bedside studies could be made. Vectorcardiographic loops were recorded on XXX Kodak 35-mm. film, including the entire QRS loop with the P and T loops or, where abnormal initial forces were obvious or suspected, isolated amplified segments of the QRS loops. The loops were interrupted 400 times per second so that consecutive tear-shaped dashes were separated from one another by 0.0025 second. Thus, four dashes and their intervals are the equivalent of 0.01 second. The tear-shaped dashes pointed with their sharp end in the direction of rotation. After processing, the films were read on a Documat Microfilm Reader (Model F), with a protractor and scale. For example, the direction of the 0.01-second vector was determined by connecting the null-point with the leading edge of the fourth tear-drop, recording the point where this line intersected the angular scale. Similarly, the maximum QRS vector was computed by connecting the null-point with the farthest point of the loop. The observed values were expressed in degrees measuring from 0 to 360° in a clockwise direction (fig. 1). An average error of 5° was assumed to be inherent in the recording and reading of the films.

Subsequently the readings were compared, and clinical charts and autopsy protocols were studied in detail, not only with reference to the particular period of hospitalization during which these cardiographic observations were made, but also in relation to the medical history, electrocardiograms, and vectorcardiograms recorded during previous admissions. In certain instances records from other hospitals were examined.

Criteria for Vectorcardiographic Diagnosis of Myocardial Infarction

No large-scale observations have been published on the vectorcardiogram with the cube technic in normal individuals. It has been observed[10, 11] that there is considerable variability in the configuration of the loop as recorded by the cube system from person to person and from time to time in the

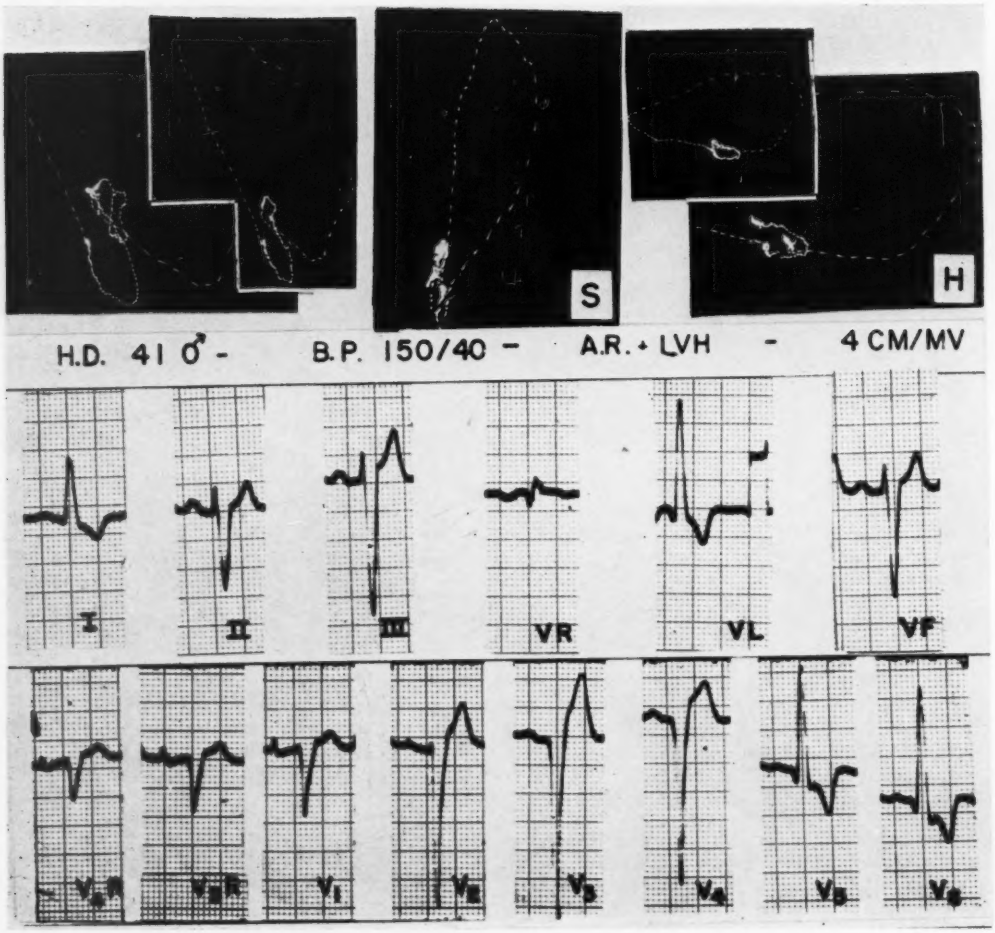

Figure 5

Discrepancy between electrocardiogram and vectorcardiogram. Left ventricular hypertrophy shown by each technic. The electrocardiogram indicates anteroseptal infarct and, according to Grant's criteria,[18] anterolateral peri-infarction block. Vectorcardiogram shows 0.01-second vector at 10° and the 0.02-second vector at 14° in the horizontal plane; this is evidence against antero-septal infarct. Left ventricular hypertrophy but no infarct demonstrated post mortem.

same person. Furthermore there appears to be some overlap between normal and borderline abnormal loops.. However, from the data of Grishman,[8] Scherlis et al.[15] and indirectly from the studies in normal subjects by the Duchosal double cube,[16] certain general formulations regarding the normal seem justified. With these data serving as controls the following topographic classification for infarcts was established for the purpose of this study (figs. 2 and 3).

1. *Anteroseptal infarct* was considered to be present if the initial forces following the 0.01-second vector were directed posteriorly to the 0° to 180° axis in the horizontal plane and posterior to the vertical axis (+90° to +270°) in the sagittal plane.

2. *Anterolateral infarct* was diagnosed with clockwise rotation of the horizontal plane loop, if the 0.01-second vector was directed rightward and the 0.02-second vector posteriorly.

Table 1

Direction of Selected Instantaneous Vectors in 62 Patients with Anteroseptal Myocardial Infarct Related to Direction of Rotation

Rotation	No. cases Total	Autopsied	Vector in degrees 0.01 sec.	0.02 sec.	max.
Horizontal plane (A)					
Entirely CCW	36	(6)	349 (327)	337 (351)	323 (337)
Short initial CW, predom. CCW	18	(3)	291 (338)	306 (351)	336 (343)
CW	8	(4)	312 (303)	335 (315)	238 (236)

Rotation	No. cases Total	Autopsied	Vector in degrees 0.01 sec.	0.02 sec.	0.03 sec.	max.
Sagittal plane (B)						
CCW	33	(7)	66 (51)	55 (36)	20 (23)	350 (349)
CW – CCW (figure-of-eight)	13	(2)	307 (310)	1 (326)	23 (359)	338 (19)
CW	13	(4)	269 (10)	286 (22)	308 (6)	12 (60)
CCW but no values	3	—	—	—	—	—

CW, clockwise; CCW, counterclockwise.

3. *High lateral wall infarct.* Here it was required that the 0.01- and 0.02-second vectors, regardless of the direction of their rotation, be located between +90° and +180° in the horizontal plane.

4. *Diaphragmatic infarct and apical infarct.* The diagnosis was made if any one of the following three criteria was fulfilled:

a. Orientation of the 0.02- and 0.03-second vector between 270° and 0° in the frontal plane.

b. Rotation of the frontal plane loop in a clockwise direction when the maximum QRS vector lay between 270° and 35°. Normally when the maximum QRS vector lies in this range, the loop rotates in a counterclockwise direction.[8, 15, 16]

c. Location of the 0.02- and 0.03-second vector between 180° and 270° in the sagittal plane.

5. *Posterobasal infarct.* Here it was required that more than 50 per cent of the QRS loop be located anterior to the 0° to 180° axis in the horizontal plane and anterior to the 270° to 90° axis in the sagittal plane and that the loop rotate in a counterclockwise direction in the horizontal plane.[17]

When infarction occurred in more than one topographic area, the vectorcardiographic findings are described separately under the appropriate categories. Thus the total number of infarcts described exceeds the number of patients.

Results

1. *Anteroseptal infarct.* The vectorcardiograms of 62 patients fulfilled the criteria for anteroseptal infarct set forth above. Of these, 13 were subsequently examined post mortem (figs. 4 and 5). The average direction of the 0.01, 0.02, and maximum vectors are given in table 1A and B. All 13 autopsied cases showed anatomic evidence of at least anteroseptal infarct. Nine of these showed infarction elsewhere (six apical and one each posterolateral, true posterior, and anterolateral).

Fifty-four of the 62 cases demonstrated counterclockwise rotation in the horizontal plane, 18 after a very short initial clockwise and posterior segment usually of 0.01-second duration. Of the 13 autopsied cases nine rotated counterclockwise, three after such a short clockwise and posterior segment. In each of these three cases the anteroseptal infarct extended to a slight degree into the contiguous lateral or apical areas.

The remaining eight cases demonstrated clockwise rotation in the horizontal plane. Four of them came to autopsy. Two showed apical involvement of pronounced degree by the infarct; the remaining two differed from the others in showing prominent involvement of the mid-portion of the septum. Of the five non-autopsied cases that showed clockwise rotation in this plane, four exhibited associated vectorcardiographic evidence of apical or

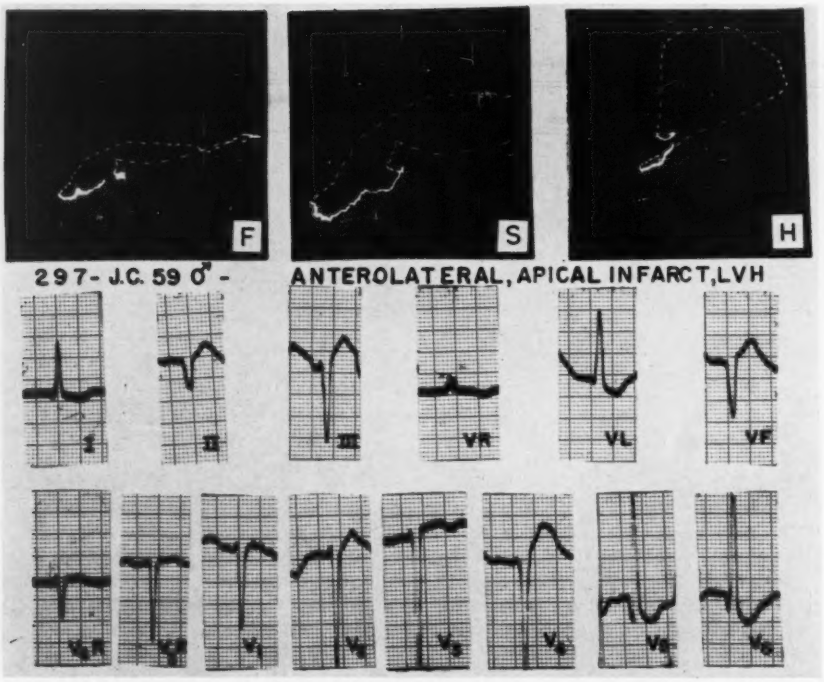

Figure 6

Significance of rotation in the sagittal plane in evaluation of multiple infarction. Vectorcardiogram shows clockwise rotation of initial vectors in all planes. In the horizontal plane the 0.01-second vector is at 160°, the 0.02-second vector at 178°. The initial vector would have been counterclockwise in the sagittal plane if there were no apical infarct. The latter is indicated by superior displacement of initial vectors in frontal and sagittal plane. Transmural anterolateral infarction with circumferential subendocardial extension into apex demonstrated at autopsy.

anterolateral infarction. Therefore, when the initial part of the loop does not rotate in the expected counterclockwise direction, while the remainder of the loop is quite characteristic of anteroseptal infarct, the possibility of infarction involving contiguous areas, especially the apical or anterolateral regions, should be considered.

This was even more clearly demonstrated by the findings in the sagittal plane (table 1B), where clockwise rotation of the QRS loop was found in six of the 13 autopsied cases. Three of these six had associated apical myocardial infarction. In contrast, none of the seven autopsied cases with counterclockwise rotation in the sagittal plane demonstrated apical involvement. Therefore, the presence of clockwise rotation in the sagittal plane, even in the absence of superiorly directed forces sufficient of themselves to establish the diagnosis of diaphragmatic or apical infarction, would suggest that such involvement is present. Of the 49 non-autopsied cases of anteroseptal infarction in whom the sagittal plane was studied, only nine demonstrated clockwise rotation; all of these had in addition evidence for diaphragmatic infarction.

Comparison between autopsied and non-autopsied cases with counterclockwise rotation showed close agreement between the values at each of the instants studied (tables 1A and B). This suggests that the observations made

Table 2

Direction of Selected Instantaneous Vectors in 44 Patients, 22 with Anterolateral and 22 with Lateral Wall Infarct, Related to the Direction of Rotation (Horizontal Plane)

Rotation	No. cases Total	Autopsied	Vector in degrees 0.01 sec.	0.02 sec.	max.
Anterolateral infarct (A)					
Clockwise	19	(3)	216 (207)	285 (218)	309 (321)
Counterclockwise	3	(2)	230 (357)	315 (355)	206 (165)
Lateral wall infarct (B)					
Clockwise	5	(4)		Wide scatter	
Counterclockwise	17	(3)	163 (160)	113 (154)	347 (325)

in the patients studied at postmortem examination may be representative of the larger group of observations in the non-autopsied material.

Observations were also made for the frontal plane loop. Since none of these fell outside of the range of normal, they are not reported here. The presence of associated left ventricular hypertrophy changes the observed values very little.[18] The anticipated variations will be discussed in more detail in the subsequent communication.[19]

2. *Anterolateral infarct.* In the 22 patients with vectorcardiographic evidence of anterolateral infarct two types of horizontal plane loop were seen. Nineteen showed clockwise rotation with the initial 0.01- and 0.02-second vector to the right of and posterior to the null-point and the maximum QRS vector in the quadrant between 270° and 360° (fig. 6). In the remaining three cases the loop had a peculiar appearance in that it rotated in a counterclockwise direction to the left for a small portion of its sweep, then continued its counterclockwise course, placing the bulk of the loop to the right of and anterior to the null-point (table 2). Again a rather close correlation between the values observed in those cases examined post mortem and the non-autopsied cases was observed. Thus the hallmark of the QRS loop in anterolateral infarction was clockwise rotation in the horizontal plane with a marked rightward direction of the 0.01- and 0.02-second vectors.

The differentiation between anterolateral infarct on the one hand and anteroseptal infarction with clockwise rotation in the horizontal plane on the other (eight out of 62 cases) therefore is determined by the direction of the 0.01- and 0.02-second vectors (fig. 6). In the non-autopsied cases of anterolateral wall infarction these were located at 216° and 285° respectively, while the corresponding values for anteroseptal infarction with clockwise rotation were 312° and 335°. These differences were even more striking in the autopsied cases (tables 1A and 2A). There was no significant difference between the maximum QRS vectors in infarcts in either of these areas.

Study of various instantaneous vectors in the sagittal and frontal planes did not yield any consistent results. In an occasional case the frontal plane loop proved helpful because of counterclockwise rotation in the presence of right axis deviation. Since the findings in the horizontal plane are so typical and so striking, it may be concluded that study of the 0.01- and 0.02-second vectors in the horizontal plane and the direction of rotation are sufficient for the diagnosis of anterolateral wall infarction.

3. *Lateral wall infarction.* The findings in the seven autopsied and in the 15 non-autopsied cases were difficult to tabulate because in most instances the lateral wall infarct was only part of a larger area of infarction. The autopsied patients who had predominant lateral wall involvement demonstrated extensive rightward displacement of the initial forces in the horizontal plane (table 2B) with the 0.01-second vector at 160° and the 0.02-second vector at 154°. In four of these the horizontal plane loop continued to rotate in a counter-

Table 3

Distribution of Diaphragmatic Infarcts and Apical Infarcts Related to Duration of Superiorly Directed Forces and Direction of Rotation in Frontal Plane

	Rotation	Autopsy	No. cases	Number with superior forces lasting 0.0225 to 0.0274 sec.	0.0275 to 0.0299 sec.	0.030 sec. or more	Average direction of max. QRS vector°	Peripheral distortion of loop ("bites")
A	Maximum QRS plus 270° thru 0 to 20° clockwise	Yes	(6)	1	0	5	331	3
		No	47	5	4	38	351	21
B	Maximum QRS 20 to 60°	Yes	(3)	1	0	2	41	0
		No	33*	7†	11	12	30	8
C	Counter-clockwise	Yes	(6)	0	0	6	68	2
		No	3	0	0	3	10	0
	Total		98† (15)	14	15	66	—	34

*Includes three cases, none autopsied, showing pronounced "bites" in frontal and sagittal planes, but not otherwise fulfilling criteria in text.

†These cases are included because their sagittal plane loop showed superiorly directed forces lasting 0.0275 to 0.0299 second.

clockwise fashion in front of the null-point and then demonstrated a marked reduction from the usual size of the loop with displacement toward the 90° to 270° axis. Similar rotation and loop configuration was observed in the non-autopsied material. Of the three autopsied patients with clockwise rotation in the horizontal plane two showed contiguous posterior and diaphragmatic infarction, and one anteroseptal subendocardial infarction.

Analysis of the data in the frontal plane yielded no consistent results.

4. *Diaphragmatic infarction and apical infarction.* Diaphragmatic and apical infarcts are grouped together in this study, since with the cube system of registration the difference between the direction of the initial vectors in both the frontal and the sagittal planes was not sufficient to warrant separation into two distinct groups.[19]

There were 98 cases of whom 15 came to autopsy (tables 3 and 4). The most important finding in these 15 was a prolongation of the superiorly directed initial QRS forces in the frontal or sagittal plane. Regardless of the initial direction of rotation of the loop, this measured 0.0300 second or more in 13 and 0.0225 second in the remaining two. If these initial forces lasted less than 0.0275 second the diagnosis of this type of infarction was not considered justified.[20, 22] One of the latter two cases, however, demonstrated a second diagnostic feature, also present in six other autopsied cases, i.e., the presence of clockwise rotation of the QRS loop in the *frontal plane* when their maximum QRS vector was located in the segment between 270°, proceeding clockwise to 20° (table 3A) (figs. 7 and 8). The remaining 83 non-autopsied cases showed a similar distribution in the abnormality of the initial superior forces. These lasted at least 0.0275 second in all but 12 cases (tables 3A and B). The remaining patients (table 3C) demonstrated counterclockwise rotation in the frontal plane. Six of these came to autopsy; every one of these showed associated anterolateral or posterolateral infarction. All six had superiorly directed forces of 0.030 second or more. The average direction of the maximum QRS vector was 68°, which is beyond the range in which counterclockwise direction of the frontal plane is normally observed. There were three non-autopsied cases in this group; all had superior forces of 0.03 second or more and demonstrated additional evidence for lateral wall infarct in other planes.

According to Young et al.[16] the extent of the initial superiorly directed forces in normal individuals studied by the Duchosal sys-

Table 4

Distribution of Diaphragmatic and Apical Infarcts Related to Duration of Superiorly Directed Forces and Direction of Rotation in Sagittal Plane

Rotation	Autopsy	No. cases	Number with superior forces lasting 0.0225 to 0.0274 sec.	0.0275 to 0.0299 sec.	0.030 sec. or more	"Bites"
Clockwise	Yes	(12)	0	1	11	4
	No	56	10*	7	39	29
Counterclockwise	Yes	(2)	1	0	1	1
	No	21	5†	6	10	0
Total		91‡ (14)	16	14	61	34

*Seven included because of decisive evidence in frontal plane.

†Included because of decisive evidence in frontal plane.

‡Total differs from that in table 5, since no observations were made in the sagittal plane of the remaining seven cases.

tem depends on the direction of the maximum QRS axis in the frontal plane. Thus, with a maximum QRS of 55° or more in the frontal plane clockwise rotation was observed, and the duration of initial superiorly directed forces was found to be 0.0275 second or less. As the maximum QRS vector becomes more horizontal the extent and duration of initial superiorly directed forces decreases. Counterclockwise rotation of the frontal plane loop becomes the rule when this axis is less than 18°. Grishman[8] in his discussion of normal controls studied by the cube system states that rotation in the frontal plane is usually counterclockwise if the maximum QRS vector is less than 35°. With the maximum QRS vector greater than 35° on the other hand, rotation is invariably clockwise. When the direction of the maximum QRS vector in the frontal plane ranges between 15° and 75° a number of normal individuals demonstrate a figure-of-eight rotation or extremely narrow loops. We were able to confirm Grishman's observation that clockwise rotation of the normal frontal plane loop never occurs when the maximum QRS vector points in a direction more horizontal than 20°.

It is clear then that in 53 instances (table 3A) the diagnosis of diaphragmatic or apical infarction could be made solely on the basis of clockwise rotation of the frontal plane loop, a consequence of the abnormally directed initial forces (fig. 8). It is to be emphasized, however, that most of these cases *also* showed superiorly directed forces, with a duration equivalent to the standard electrocardiographic criteria of a Q_3 and Q_aV_F measuring 0.03 second (figs. 6 and 7).

Furthermore, 34 patients demonstrated an interesting finding in the peripheral part of the QRS loop, consisting of a sudden deviation of the loop ("bite"), which had been inscribed smoothly up to that point (figs. 7 and 8). This finding was considered significant only when present in both the frontal and sagittal planes. The interruption occurred at a time when depolarization of the outer layers of the myocardium in the diaphragmatic and apical area would be expected.[20-25] Indeed in the three cases examined microscopically that demonstrated this phenomenon, the infarct extended to the epicardium. The frequency of this observation (34 of the entire group of 98 cases) indicates that considerable significance should be attached to this finding.[5, 19]

In the *sagittal plane* counterclockwise rotation is normal for all control series reported[8, 26] (table 4). Therefore the presence of clockwise rotation by itself is abnormal. This was found in 12 autopsied and 56 non-autopsied cases. In seven of the 12, associated anteroseptal or anterolateral wall infarction was demonstrated, and lateral wall involvement in the remaining five. The opposite was observed in the two autopsied cases with counterclockwise rotation in the sagittal plane; involvement of the posterior or posterolateral wall, rather than the anterolateral region, was present. Furthermore, of the 56 non-autop-

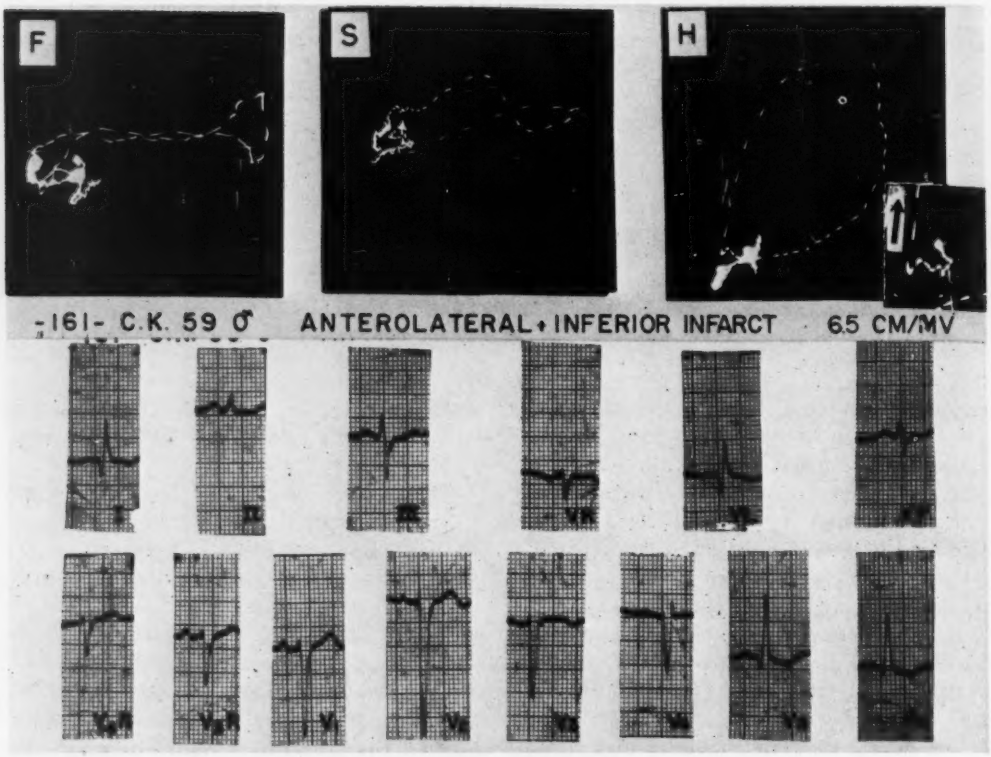

Figure 7

Value of sagittal plane in multiple infarction. Here the diaphragmatic component of infarct was demonstrated only in vectorcardiogram. The anterolateral component was indicated in both electrocardiogram and vectorcardiogram. Initial vectors rotate clockwise in all planes and show large superior displacement in frontal and sagittal planes. This loop differs from that of left bundle-branch block (fig. 9) in the clockwise rotation of its initial component in the horizontal plane (see insert in horizontal plane) and in the absence of delay in its total duration.

sied cases with clockwise rotation 35 revealed additional evidence of anteroseptal or anterolateral wall infarction in the horizontal plane loop. This suggests that clockwise rotation in the initial portion of the sagittal plane loop, not only indicates infarction of the inferior region of the heart, but in the majority of instances it signifies involvement of the anterior or anterolateral wall of the left ventricle as well[19] (figs. 6 and 7).

In summary, the detection of clockwise rotation in the frontal or in the sagittal plane and the measurement of the maximum QRS vector are both so simple and accurate and their reliability as demonstrated in the autopsied cases is so striking, that it should be considered the most important criterion on which the presence of diaphragmatic or apical infarction can be determined. This was present in 68 of the 98 patients with this type of infarction. In 22 of the remaining 30 cases the duration of superiorly directed initial forces, whether rightward or leftward, was 0.0275 second or more, irrespective of rotation of the remainder of the loop. This corresponds in significance to the measurement of a wide and deep Q wave in leads III and aV_F of the standard electrocardiogram.[27, 28]

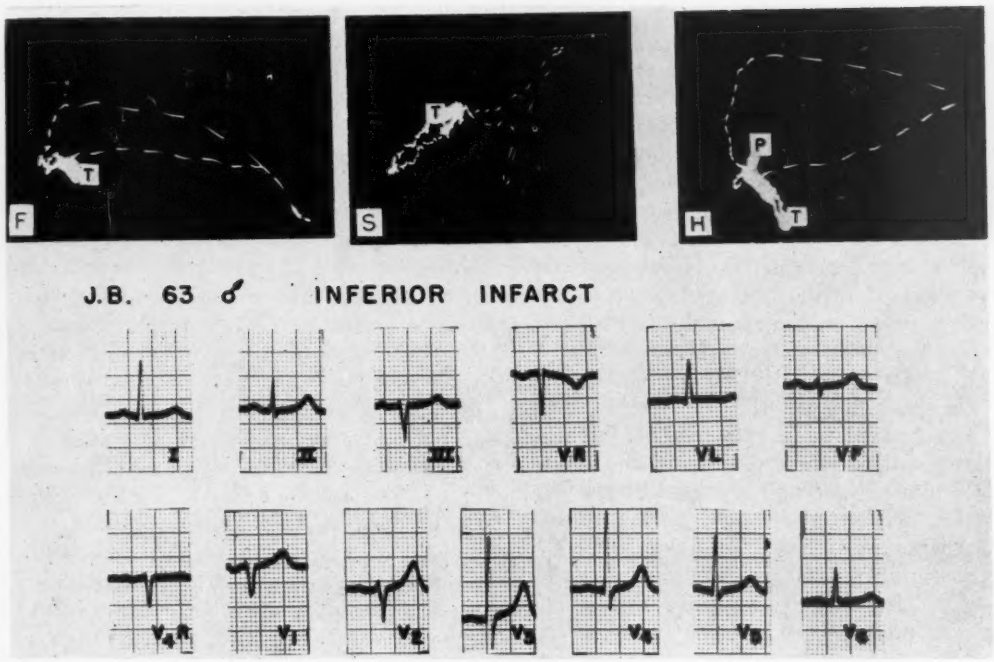

Figure 8

Inferior myocardial infarction. Clockwise rotation of initial segment of frontal plane loop in association with superior displacement of maximum QRS axis (+10°) establishes the diagnosis. Inferior infarct is not obvious in electrocardiogram. The patient had a classical clinical episode with markedly elevated lactic acid-dehydrogenase levels (> 400 units). P- and T-wave loops are indicated in figures.

With an occasional exception the precision and ease with which the short time interval of 0.0275 second to 0.030 second can be measured in an oscilloscopic recording is preferable to similar measurements made in the ordinary electrocardiogram. Furthermore, the data recorded in the sagittal plane are not easily visualized in the standard electrocardiographic tracing. These considerations explain many of the discrepancies found between the standard electrocardiogram and vectorcardiogram (table 5, figs. 7 and 8).

5. *Posterobasal infarction.* There were 13 clinical and nine postmortem cases showing posterobasal ("true posterior") infarction. In only two of the nine autopsied cases and one of the 13 clinical cases was this infarct limited to the posterobasal region. In nearly all of the remaining cases infarction was also demonstrated post mortem or by vectorcardiographic criteria in the diaphragmatic or lateral aspects of the heart. In the horizontal plane most showed the greater bulk (more than 60 per cent) of the QRS loop to be located anterior to the 0°-to-180° line. Counterclockwise rotation occurred in this plane in seven of the nine autopsied cases; the direction of their 0.03-second vector was at 30°, and of the 0.04-second vector at 14°. Similar rotation and similar direction of the 0.03- (32°) and 0.04-second vectors (9°) was found in 11 of the 13 non-autopsied cases.

Discussion

Findings at Postmortem Examination

One of the most significant findings in the autopsied cases was the infrequency of infarcts involving a single topographic area. Of

the 43 cases examined post mortem only 16 showed such a discrete infarct; 19 showed either two infarcts or a large infarct extending into more than one region. The remaining eight demonstrated more than two infarcts. Indeed, the 16 showing single infarcts presented a vectorcardiogram that was considered "classical" for infarction of that particular area. This contrasts with the complexity of the vectorcardiographic loop in the remaining cases. It is theoretically possible for a second or third area of infarction to displace or even cancel the abnormal forces expected from a single infarct (fig. 2). This is probably one of the reasons for the wide variations in some of the observed values. Nevertheless, in most instances, the vectorcardiographic loop facilitated a more vivid and graphic visualization even of multiple infarcts than did the electrocardiogram.

Excepting four instances in which there was a discrepancy between the number of infarcts predicted from the vectorcardiogram and the findings at autopsy, the QRS-loop abnormalities corresponded in all of the 45 to the findings at autopsy. In one of these four an extreme degree of diffuse necrosis of the left ventricular wall had induced a pattern of posterobasal infarct while the area of myocardial necrosis actually extended from the posterior into the lateral wall.[29] In the second case a posterobasal infarct was correctly diagnosed but an extension into the apex of the left ventricle was not detected. In the third patient a lateral wall component of an apical infarction was thought to be present but not confirmed at autopsy. In the last individual there were two discrete myocardial infarctions, one anteroseptal and the other involving the posterior portion of the septum and the contiguous posterior wall of the left ventricle. The vectorcardiogram here showed only the anteroseptal infarct. It is likely that cancellation effects account for the failure of the vectorcardiogram to detect the second infarct.

There were two additional cases, not included in this series, where a divergence was observed between the vectorcardiogram and the postmortem findings. One demonstrated a normal electrocardiogram and vectorcardiogram. At necropsy this patient showed an intramural infarct on the posterior wall of the left ventricle, measuring only ½ cm. in its greatest diameter. Classical electrocardiographic and vectorcardiographic findings for anteroseptal infarct were recorded in the second patient. She was a 37-year-old woman with rheumatic heart disease and very severe mitral regurgitation. Striking left atrial enlargement was found at postmortem examination but there was no coronary artery disease. A similar vectorcardiographic phenomenon was observed in three patients during the study with the Frank lead system. A possible explanation for these observations will be presented in the succeeding communication.[19]

Also not included in this series of myocardial infarctions were four patients in whom the electrocardiogram raised the question of a myocardial infarct. In each instance the vectorcardiogram failed to confirm this diagnosis but showed left ventricular hypertrophy in three. The patient with a normal vectorcardiogram had no heart disease. In the three whose vectorcardiograms showed left ventricular hypertrophy considerable anteriorly directed forces were noted in the horizontal plane, so that both the 0.01- and 0.02-second vectors were anterior to the 0° to 180° axis. In each of these three cases, the electrocardiogram had raised a question of an old anteroseptal infarct, either on the basis of deep QS complexes from V_1 to V_4, or of minimal R waves from V_1 to V_3, which became even smaller as the electrode was moved onto the left precordium. In each of these, autopsy revealed a severe degree of left ventricular hypertrophy; in two the result of severe aortic stenosis and, in the third, of free aortic regurgitation (fig. 5). Two of these patients had been treated for prolonged periods of time as having acute myocardial infarction because of associated R-ST-segment and T-wave changes. It is clear that in these instances the vectorcardiogram was of great value.

Conditions Simulating Myocardial Infarction

The manner in which left ventricular hypertrophy is differentiated from anteroseptal infarction,[30] anteroseptal wall infarction from

Table 5

Comparison of Vectorcardiographic and Electrocardiographic Findings

		Group A (Postmortem) Infarct	Group A (Postmortem) No infarct	Group B (Clinical)	Totals
VCG	ECG Diagnostic	24*†	2	53‡	79
Diagnostic of	ECG Questionable	9	0	8	17
Infarction	ECG Negative	10	0	9	19
VCG	ECG Diagnostic	0	1	3§	4
Negative for	ECG Questionable	0	3	0	3
Infarction	ECG Negative	0	0	0	0
Total		43	6§	73	122

*Not included in this group were four cases referred to on page 820 in which precise localization of infarcts was inaccurate.

†Included in this group were three cases in which electrocardiogram showed only a single infarct while vectorcardiogram correctly localized more than one area of necrosis as found at postmortem examination.

‡Included in this group were 10 non-autopsied cases in which vectorcardiogram showed more than one infarct while the electrocardiogram indicated only one.

§The total number of patients indicated in this chart differs from that in groups A and B as presented in text because cases in which VCG or autopsy showed no infarct are included, when there was a discrepancy between VCG and ECG.

giant right atrium,[20] and right ventricular hypertrophy of minor degree from true posterobasal infarction is discussed in the subsequent publication.[19]

Left bundle-branch block can be differentiated from anterolateral infarction on the basis of the following considerations. In left bundle-branch block clockwise rotation in the horizontal plane is preceded by a short but definite initial anterior counterclockwise segment lasting approximately 0.010 to 0.012 second. Such an initial component was observed in all of our cases and in 21 of 25 cases studied by Frimpter et al.[31] by the Frank system. In addition, in left bundle-branch block the loop characteristically moves slowly throughout its entire sweep and the time markings are spaced closely together. Such changes are not observed in anterolateral infarction. The contrast between the vectorcardiogram of left bundle-branch block and that of anterolateral infarct is well illustrated in figures 6, 7, and 9.

There were two instances in this series where lateral wall infarction was suspected on the basis of counterclockwise rotation and excessive initial rightward forces in the horizontal and frontal planes. Each was 37 years old and each had severe aortic regurgitation. In the one autopsied case no infarction was found. The explanation for the unusual rightward and anterior forces of the spatial QRS loop in these cases may be the excessive degree of septal hypertrophy. This increased the normal vector, caused by septal depolarization, to such a degree that lateral wall infarction was simulated. However, the obvious physical signs of cor bovinum in patients with such a vectorcardiogram should lead one to suspect the correct diagnosis.

Vectorcardiographic versus Electrocardiographic Findings

In the evaluation of this technic as compared with standard scalar electrocardiography certain considerations should not be forgotten. Either of the technics is subject to two types of error, namely, the error of the method itself and the error of the individual. The former, which is integral to the technic, is the truth that this investigation seeks. But it is subject to certain human factors implicit in the art as opposed to the science of electrocardiography. Furthermore, there is the stubborn resistance of some to the acquisition of a new discipline, on the one hand, and the bias presented by the vested interest, on the other. No one happily invests 4 or 5 years of his career in a technical and intellectual problem then readily concedes its futility.

Bearing these limitations in mind an at-

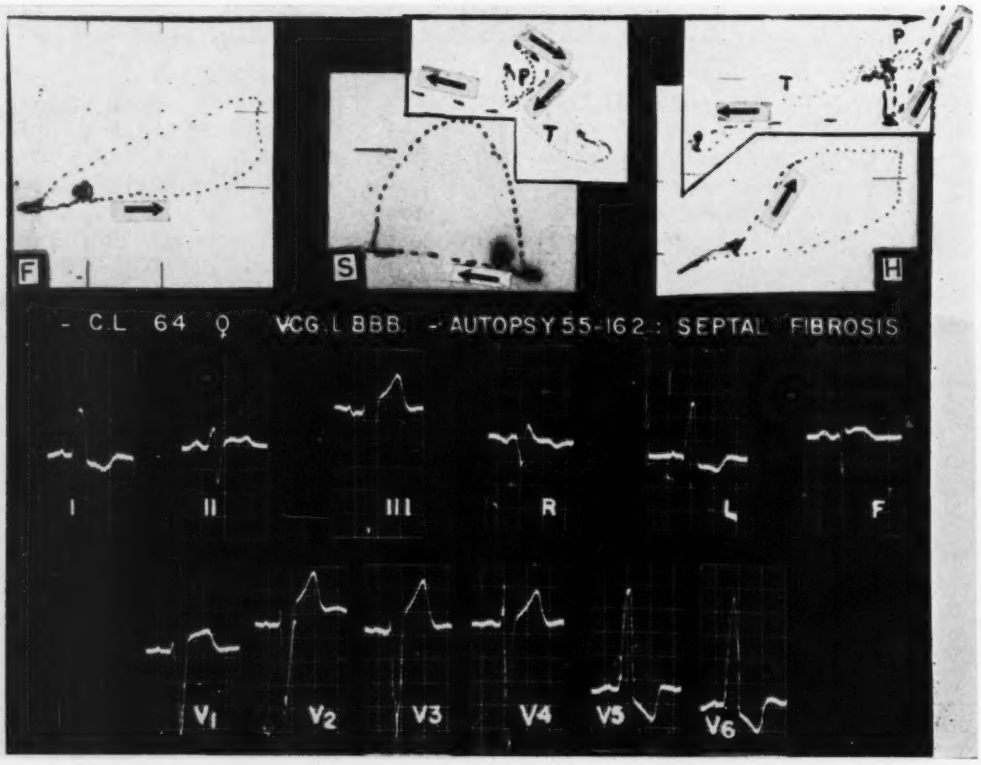

Figure 9

Left bundle-branch block. (This is the only figure presented in this communication in which the sagittal plane is viewed from the patient's right *side.) The loop moves slowly throughout its entire sweep in all planes. The initial counterclockwise rotation in the horizontal plane is best shown in the amplified insert (arrow). The total duration of the QRS in the vectorcardiogram is 0.16 second. At autopsy septal fibrosis, involving the left bundle, was found.*

tempt was made to assess the relative value of the vectorcardiogram, as recorded by the Grishman cube technic, against the standard electrocardiogram in the detection of myocardial infarction. The electrocardiograms were reviewed and interpreted without knowledge of the clinical, pathologic, or vectorcardiographic findings. The 122 cases considered were those falling in groups A and B. The results are given in table 5. The electrocardiograms of 10 of the patients in group A and of nine in group B failed to indicate myocardial infarction. In addition there were 17 patients in groups A and B whose electrocardiograms yielded only questionable evidence. In all 36 the vectorcardiogram was interpreted as indicating myocardial infarction. This was confirmed in each case that was studied post mortem (figs. 4 and 7). Such discrepancy need not be too surprising, if one considers the high incidence of undiagnosed myocardial infarction found at autopsy as reported in various series.[32] On the other hand, such a large degree of variance does come unexpected, since it has been stated[33] that the information recorded by an uncorrected lead system cannot be other than that registered by the standard electrocardiographic lead

system. Although this discrepancy may be due to the application of scalar electrocardiographic criteria that are too rigid, the alternative explanation seems more likely, namely, that even the "uncorrected" vectorcardiogram, either by virtue of the method of lead application or of the manner of registration of planar forces on the cathode ray screen, or of both, allows for more strict diagnostic criteria, and in selected cases may lead to the correct diagnosis.

Summary

A total of 161 vectorcardiograms was recorded with the Grishman cube system in patients with suspected myocardial infarction. In the group of 49 cases subsequently examined post mortem and of 73 non-autopsied cases, in whom the diagnosis of infarction appeared certain, a comparison was made between the standard electrocardiogram and the vectorcardiogram taken in succession. The vectorcardiogram demonstrated more infarcts than the electrocardiogram. Of a total of 122 cases in which the vectorcardiogram showed infarction, 19 had normal and 17 equivocal electrocardiograms. A number of simple and easily applicable criteria for the vectorcardiographic diagnosis of infarction are given. It appears that even the older, uncorrected cube-lead system permits a more accurate diagnosis than currently available standard electrocardiographic procedure. It is suggested that this method of exploration may be useful in cases of suspected myocardial infarction in which the routine electrocardiographic examination leaves doubt.

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The Early History of Instrumental Precision in Medicine

Avenbrugger lived on to see his famous colleague, De Haen, write his fifteen volumes without a word on percussion. Van Swieten did it no greater justice. In his huge history of medicine, Sprengel mentions it as rather subtile. Yet were the contents of this booklet of twenty-two pages, more practically valuable to man than all these men wrote or all the results of the vast and bloody campaigns during which it slept, until in 1808, one year before the grave, when this contented music-loving German died at 87, Corvisart translated it into French, and proclaimed its undying value to a waiting world.—S. WEIR MITCHELL, M.D., *Transactions of the Congress of American Physicians and Surgeons* held at Washington, D.C., 1891. New Haven, The Congress, 1892, p. 180.

A Clinical Appraisal of the Vectorcardiogram in Myocardial Infarction

II. The Frank System

By PAUL G. HUGENHOLTZ, M.D., CLAUDE E. FORKNER, JR., M.D., AND HAROLD D. LEVINE, M.D.

IN THE preceding communication[1] the results of the vectorcardiographic examination of 161 cases of myocardial infarction employing the cube system[2] were described. In the present report the results are given for 206 cases studied by the Frank system.[3]

The purpose of this study is to determine the practical value of this corrected lead system, which has been reported to possess many theoretical advantages over older recording systems.[4-7] In addition, a comparison between the standard electrocardiogram and the vectorcardiogram is made in a fashion similar to that described previously. On the basis of distinct correlations found in the preceding study the same system of classification of types of infarct is maintained.

Methods and Materials

These studies were carried out over a period of two years on patients hospitalized at the Peter Bent Brigham Hospital. The vectorcardiographic system used was that proposed by Frank.[3] In all other respects the technic followed that described in the previous communication. On the basis of the same criteria the material of this study was classified into three categories: Group A, namely those with *indubitable* infarction, 24 of the 35 patients who were examined at autopsy; group B *probable* infarction, 101 patients with classical sequential electrocardiographic changes and convincing evidence of tissue breakdown; and group C, *presumptive* infarction, 81 patients in whom, despite a convincing history, complete confirmation by laboratory tests was not forthcoming.

From the postmortem specimen the area or areas of infarction in a particular heart were classified topographically in accordance with the accompanying diagram (fig. 1).

Corresponding with the convention set forth in the previous publication, the QRSsÊ loop as inscribed in the sagittal plane was recorded as if the observer were looking from the left shoulder into the sagittal section of the body (see fig. 1 of preceding paper).[8, 9]

Consequently, it was necessary to reverse the values found by Pipberger[10] in the sagittal plane in normal adults in order to conform to this manner of registration (table 1).*

Criteria for Vectorcardiographic Diagnosis of Infarction

In a detailed study of 100 normal individuals, between 15 and 69 years of age, Pipberger,[10] utilizing the SVEC-III system, examined a number of vectorcardiographic parameters and determined their statistical validity. Since the direction of vectors as found by the Frank system approximates closely those registered by the SVEC-III system, his data were regarded as a standard for

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Studies carried out during tenure of Fellowships from the Massachusetts Heart Association (no. 290, Dr. Hugenholtz), the U. S. Public Health Service (HF-8886 and HF-8580-C, Dr. Forkner), and with support from Cardiac Research Fund (no. 264) Peter Bent Brigham Hospital.

Presented in part at the Thirty-third Scientific Sessions of the American Heart Association, St. Louis, Missouri, October 22, 1960.

*Only tables 2, 3, 7, and 10 are presented with this publication. Tables 1, 4, 5, 6, 8, 9, and 11 have been deposited as Document number 6776 with the ADI Auxiliary Publication Project, Photoduplication Service, Library of Congress. Copies may be secured by citing the Document number and by remitting $1.25 for photoprints, or $1.25 for 35 mm. microfilm. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.

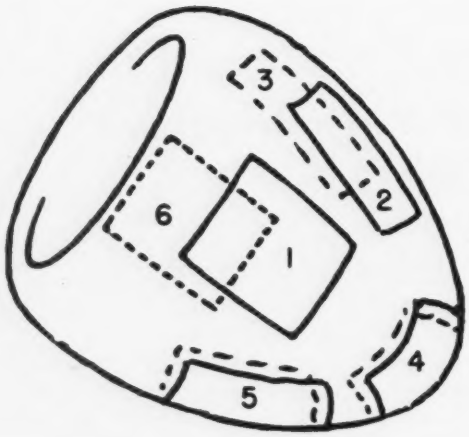

Figure 1

Schema of left ventricle, designating areas of possible myocardial infarction: (1) anteroseptal; (2) anterolateral; (3) lateral; (4) apical; (5) diaphragmatic, and (6) posterobasal. Modified after Grant, R. P., and Estes, E. H., Jr.[55]

normality in the present study. In addition, a series of normal controls in a younger age group was studied by the Frank method in this laboratory.[11] The results agreed well with those obtained with the SVEC-III technic. In this analysis particular attention was directed to the following parameters: (1) the direction of the 0.01, 0.02, 0.025, 0.03, and 0.04-second QRS vectors in the various planes, using Helm's system of notation[8] (fig. 2 of preceding publication); (2) the direction of the maximum QRS vector; (3) the direction of rotation (clockwise or counterclockwise) of the loop; and (4) the presence of abrupt changes in the direction of the middle or final thirds of the QRSsÉ loop ("bites" or "ares").[12, 13] The magnitude of the various QRSsÉ vectors was not analyzed. Accordingly, whenever the word vector is used in this text, it refers only to the projection upon a certain plane of the spatial direction of that vector.[1]

General Considerations

As outlined in the discussion of the preceding publication the most significant abnormalities of ventricular depolarization after myocardial infarction are to be found in the vectors generated within the first 0.03 second (fig. 1 of preceding publication).[14] The vectorcardiograph is particularly suited for the study of the direction of these initial vectors. The cathode ray oscilloscope allows instantaneous synthesis of rapidly changing electrical forces. In addition, a corrected lead system reduces variations and aberrations related to differences in body build, dipole position, and effective lead axes (figs. 2, 8, and 14).[7] This is borne out by the small standard deviations found in normal controls (table 1).[10, 11]

Each of the observations made at a given instant is the resultant of electrical forces generated by simultaneous depolarization of many different areas of the myocardium. For example, 0.02 second after the beginning of ventricular depolarization, the resultant vector is usually oriented inferiorly and anteriorly, toward the apex of the left ventricle. Depolarization of most of the left septal mass has been accomplished and the wave of accession is now progressing along the Purkinje system in the free wall of the left ventricle.[15] At the same time it is already proceeding from endocardium to epicardium in the neighborhood of the apex of the left ventricle. Thus, a single area of infarction in the anteroseptal region might displace the expected normal vector for this instant and would create a QRSsÊ-loop deformity "classical" for anteroseptal infarction. When multiple areas are infarcted, however, the anticipated abnormal vector may be displaced in a different direction. For example, infarction of the subendocardial and intramural laminae of the free lateral wall in *addition* to anteroseptal infarction would displace the infarct vector in a much more *rightward* direction, assuming that both areas are simultaneously depolarized. It follows that it may be difficult to predict the direction of an infarct vector when there is more than one area of infarction. This explains in part the difficulty in correlating anatomic and vectorcardiographic phenomena in multiple myocardial infarctions. The wide standard deviations found in various infarct groups must be explained in part on this basis.

Similarly, deviations of the anticipated infarct vector might be expected in the presence of right or left ventricular hypertrophy. It was found, however, that the various abnor-

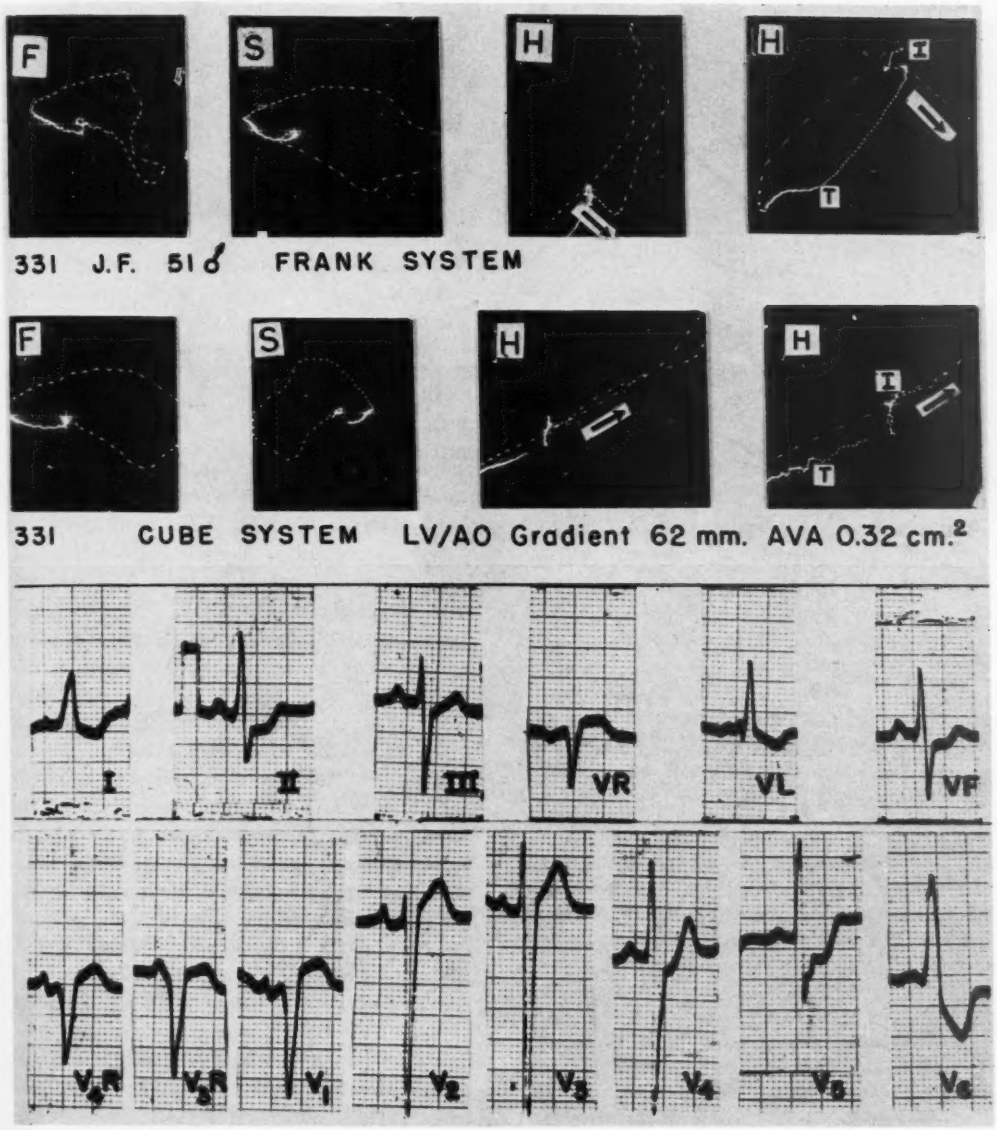

Figure 2

Disparity between cube and Frank system. (The sagittal plane in the lower row [cube] is viewed from the right.) Sagittal and horizontal plane loops show an anteriorly directed force of 0.0275-second duration (11 × 0.0025 sec.) by the Frank technic, no anterior force by the cube technic. The 0.02-second vector in the horizontal plane is at 30° by Frank, 335° by cube. Each system shows marked posterior and leftward deflection of the peripheral QRS loop, indicating left ventricular hypertrophy. The patient was a 51-year-old man with aortic stenosis. Autopsy showed no myocardial infarction. (The right-hand frames are an amplification of initial and terminal QRS forces in the horizontal plane. I represents the isoelectric or null-point; T denotes T loop.)

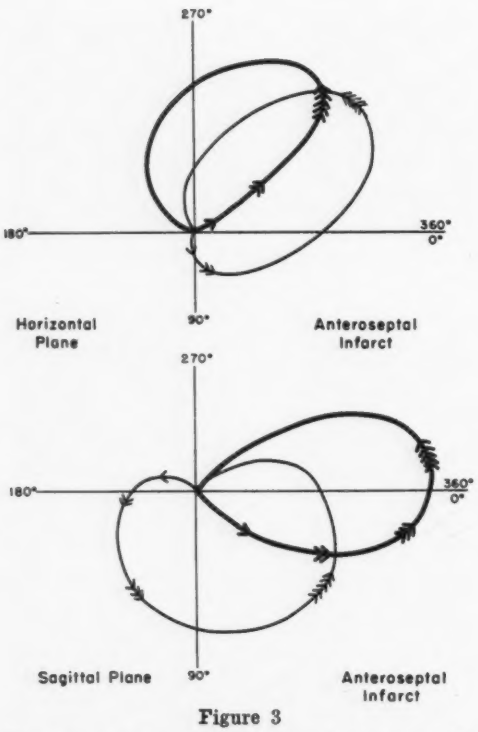

Figure 3

Diagram of average QRSsÊ loop in patients with anteroseptal myocardial infarction (heavy line) contrasted with normal controls (light line) in horizontal and sagittal planes. Note the marked difference in direction of the 0.02-second vector between patients with anteroseptal infarct and normal controls (cf. table 2). In this and succeeding figures arrows indicate direction of rotation and location of instantaneous vectors in accordance with the following scheme:

average vector at 0.01 second;
average vector at 0.02 second;
average vector at 0.025 second;
average vector at 0.03 second;
average vector at 0.04 second; and
average maximum vector.

mal initial vectors were actually influenced very little by concomitant hypertrophy. A possible explanation for this observation may be that with left ventricular hypertrophy the abnormally large vectors directed posteriorly and to the left are usually manifested somewhat later in the period of ventricular activation.[16–18] Therefore, they would not be expected to affect the forces generated between 0.01 and 0.025 second. For right ventricular hypertrophy, similar reasoning may be advanced.[19] Changes caused by left bundle-branch block have been discussed previously.[1]

Finally, it needs to be reiterated throughout this discussion that, although abnormalities in depolarization are present in three dimensions, our emphasis is placed, at times, on the reflection of these vectors upon a single plane when that projection appears best to indicate abnormality.

Vectorcardiographic Observations

The results of this study are given in tables 2 to 10. Selected data are discussed in detail in the following section.

Anteroseptal Myocardial Infarction

Forty-eight patients were considered to have anteroseptal myocardial infarction; seven of these were examined post mortem. The values for the 0.01- and 0.02-second and maximum QRS vectors in the *horizontal* plane are given in table 2. Forty-four of the 48 showed counterclockwise rotation in this plane. The average direction of the 0.02-second vector (322°) for the non-autopsied cases corresponded closely with that of the seven autopsied cases (312°). Furthermore, the measurements for this vector fall within a very narrow range (S.D. 32.4°). When compared with the direction of the normal vector for this instant, there appears to be no overlap ($p < 0.001$) (fig. 3). This contrasts with the wide standard deviation of 79.5° found for the 0.01-second vector. Such a wide range of values may be partially explained by the fact that in many instances the wave of depolarization may at 0.005 second not yet have reached the area of infarction. Therefore it would retain a normal anterior and rightward direction.[20–23] By 0.010 second the vector has usually been displaced posteriorly as a result of the infarct. However, there were several cases in which significant displacement was not recorded at this moment of ventricular depolarization, resulting in a wide spread of observations (cf. figs. 4 and 5 with 12). Therefore the 0.02-second vector in these instances

Table 2

Mean Values (in Degrees) of Selected Instantaneous Vectors in 44 Cases with Anteroseptal Myocardial Infarction with Counterclockwise Rotation in Horizontal Plane

Plane and rotation	No. cases Total	Autopsied	0.01 sec.	S.D. S.E.	0.02 sec.	S.D. S.E.	0.03 sec.	S.D. S.E.	Maximum vector	S.D. S.E.	"Bites" No. cases
Horizontal counterclockwise	44	(7)	326 (296)*	79.5 *11.9*	322 (312)	32.4 *4.9*	—	—	323 (307)	36.3 *5.5*	15
Sagittal counterclockwise	30	(4)	39 (82)	70.9 *12.9*	33 (60)	55.2 *10.1*	15 (17)	42.9 *7.8*	342 (339)	44.3 *8.1*	11
Sagittal clockwise	14	(3)	314 (312)	45.7 *12.3*	338 (322)	43.8 *11.7*	3 (357)	32.5 *8.7*	18 (23)	24.3 *6.5*	4

*In this and subsequent tables the standard deviation (S.D.) is given in roman type, the standard error of the mean (S.E.) in italics. The latter has not been computed where the number of observations was less than 10.

has greater significance than the 0.01-second vector. Similar observations were made by Howitt and Lawrie,[24] using the cube system. Obviously the finding of a 0.005- and 0.010-second vector, both directed posteriorly and to the left, still indicates infarction but suggests its location in the high anteroseptal mass closer to the origin of the left bundle[25] (fig. 5).

There is no difference between the direction of the maximum QRS vector (323°, table 1) in the horizontal plane in normal individuals and that in 44 patients with anteroseptal infarction (323°, table 2). Furthermore, the standard deviations for both groups of observations are very similar (40.6° and 36.3°). Therefore in anteroseptal infarction the peripheral segment of the QRSsÊ loop is not displaced posteriorly. This is another helpful point in the differentiation from left ventricular hypertrophy, in which condition such displacement usually occurs.[14, 16]

In 30 of the 48 cases of anteroseptal infarction the *sagittal* plane QRSsÊ loop rotated in a counterclockwise direction (table 2, figs. 3 and 4). Again a rather wide variation of the 0.01-second vector (39°, S.D. 70.9°) was observed. There was also poor agreement between the autopsied (82°) and the non-autopsied cases (39°). The 0.02-second vector (33°, S.D. 55.2°) corresponded more closely with the mean value of the necropsied group (60°). The 0.03-second vector was tabulated here because of the excellent correspondence with the mean value in cases in which the anatomic site of the infarct was definitely known (15° vs. 17°). Moreover, the standard deviation was smaller in this group (42.9°). Furthermore, the maximum QRS vectors (349° vs. 339°) was quite similar in both groups. All these measurements differ significantly from their normal counterparts ($p < 0.001$).

Of the 44 with counterclockwise rotation in the horizontal plane 14 demonstrated clockwise rotation in the sagittal plane (fig. 5). In autopsied and non-autopsied cases in this group there was a close correlation for all vectors measured (table 2). In the three cases examined post mortem the anteroseptal infarct extended into the apical region (fig. 5). Moreover, other vectorcardiographic evidence for associated apical or diaphragmatic infarct was present in nine of the 11 non-autopsied cases with clockwise rotation. Conversely, the diagnosis of concomitant apical infarction could be made in only one of the 30 previously described cases with counterclockwise rotation in the sagittal plane (table 10).

In conclusion, it appears that measurement of the 0.01- and particularly of the 0.02-second vectors in the horizontal plane and the 0.03-second vectors in the sagittal plane is essential for the diagnosis of anteroseptal infarction. Absence of significant anteriorly directed forces constitutes the most reliable evidence for this diagnosis. If clockwise rotation oc-

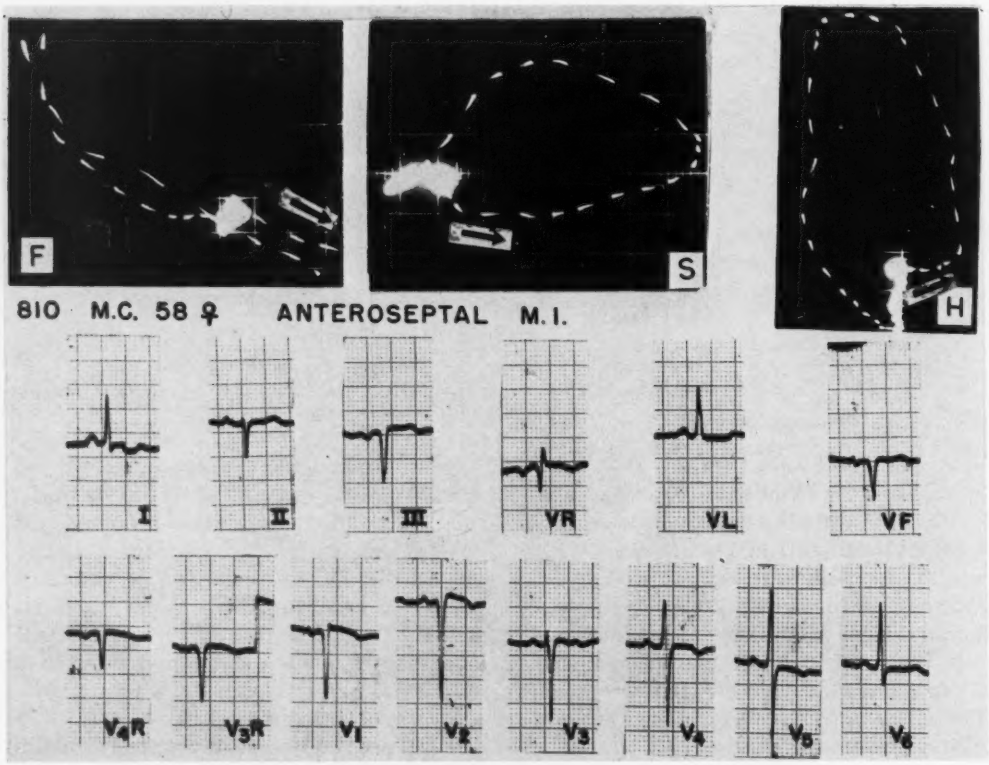

Figure 4

Anteroseptal infarction, displacing earliest (0.01 second) vector. In the vectorcardiogram in the horizontal plane the 0.01-second vector was at 352°, the 0.02-second vector at 300°; in the sagittal plane the direction of rotation of the loop was counterclockwise, the 0.01-second vector at 60°, the 0.02-second vector at 13°. Electrocardiogram suggests, vectorcardiogram is diagnostic of anteroseptal infarct. Electrocardiogram is in line with, vectorcardiogram incompatible with, diaphragmatic infarct. Extensive anteroseptal infarction; no diaphragmatic infarct found at autopsy. In this and the following illustrations the direction of rotation is indicated by the direction in which the tapering end of the teardrop points.

curs in the sagittal plane, associated diaphragmatic or apical infarction must be given serious consideration (cf. fig. 4 with figs. 5 and 10).

Anterolateral Myocardial Infarction

A total of 31 cases was available for analysis. Six of these were examined post mortem. Every case in this group showed clockwise rotation in the *horizontal* plane, a finding never observed in normal subjects[10, 11] (fig. 6, table 3). Furthermore, in the first 0.01 second the vectors had a rightward and slightly anterior direction (178°, S.D. 68.3°). The explanation for this wide standard deviation is probably the same as that already given for the similar observation in anteroseptal infarction. In view of the overlap with normal subjects, therefore, the direction of the 0.01-second vector is not decisive. However, the loop continued in a rightward direction in all cases; this was never observed in normal controls. The discrepancy in the direction of the 0.02-second vector when compared with the

Table 3

Mean Values (in Degrees) of Selected Instantaneous Vectors in 31 Cases with Anterolateral Myocardial Infarction

Plane and rotation	No. cases Total*	Autopsied	0.01 sec.	S.D. S.E.	0.02 sec.	S.D. S.E.	0.03 sec.	S.D. S.E.	Maximum vector	S.D. S.E.
Horizontal clockwise	31	(6)	178 (173)	68.3 *12.3*	241 (261)	43.3 *6.0*	—	—	307 (296)	24.2 *4.4*
Sagittal counterclockwise	12	(2)	87 (79)	75.0 *21.7*	44 (83)	42.1 *9.3*	28 (54)	20.8 *6.0*	17 (33)	28.1 *8.1*
Sagittal clockwise	14	(4)	296 (242)	85.9 *23.0*	313 (288)	62.8 *16.8*	4 (347)	17.5 *4.7*	2 (33)	62.7 *16.8*

*Total number of observations for each plane is not identical in this and subsequent tables because of exclusion of technically unsatisfactory recordings.

normal (241° vs. 84°) ($p < 0.001$) indicates that this measurement is the next most important criterion for the diagnosis of anterolateral infarction (fig. 6).

Some influence on the direction of the maximum QRS vector should be expected, since the depolarization of the anterolateral region occurs later than that of the anteroseptal area[20-23] and therefore would be more likely to influence peripheral loop configuration. This is illustrated by the observed values for the maximum QRS vector (non-autopsied 307°, autopsied group 296°). However, the differences between these measurements and those observed in normal controls (323°), although significant ($p < 0.01$), were less impressive.

Only a limited number of observations were made for the *sagittal plane;* they were about equally divided into two groups, one rotating counterclockwise and the other clockwise. In 15 of 19 instances of clockwise rotation in the sagittal plane additional vectorcardiographic evidence was at hand for apical or diaphragmatic involvement. In all four autopsied cases with this finding the infarct actually involved these additional areas (table 10). Conversely, in the two post mortem cases with counterclockwise rotation in this plane, associated apical or diaphragmatic infarction could not be demonstrated. In only two of the 12 nonautopsied cases with counterclockwise rotation in the sagittal plane, was there other evidence for apical or diaphragmatic infarction.

The most significant finding in the *frontal plane* QRSsÊ loop was a distinct preponderance of counterclockwise rotation, even in the presence of a nearly vertical maximum QRS axis. However, in this group none of the early vectors was of diagnostic importance because of the wide spread in the normal values for the 0.01- and 0.02-second vectors in this plane. In contrast to this the group with clockwise rotation showed significant superior displacement of the 0.03-second vector (315° vs. 339° for autopsied cases). This is probably best explained by the observation that in the four cases coming to autopsy associated apical infarction was present (table 3).

In summary, it is evident that the most reliable criterion for anterolateral infarction is clockwise rotation in the horizontal plane. The second most helpful evidence was rightward displacement of the 0.01-second (178°) and the 0.02-second vectors (241°). This suggests that in anterolateral infarction abnormal forces exert their maximal influence slightly later in the sequence of depolarization than in anteroseptal infarction, and thereby cause a reversal of the normal direction of rotation. Associated infarction of the apical region is frequent[25] and can be demonstrated by clockwise rotation of the sagittal plane loop. The frontal plane is often helpful in that it may demonstrate counterclockwise rotation, with rightward displacement of the initial forces.

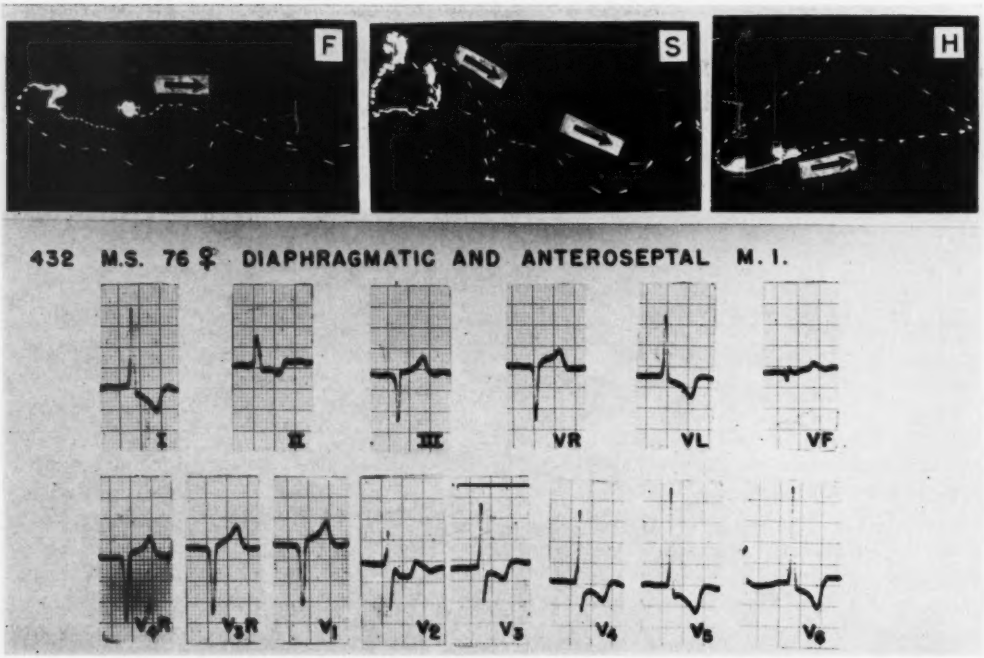

Figure 5

Discrepancy between vectorcardiogram and electrocardiogram. Vectorcardiogram diagnostic of left ventricular hypertrophy, anteroseptal (0.01-second vector 356°, 0.02-second vector 347° in horizontal plane; 0.01-second vector 347°, 0.02-second vector 356° in sagittal plane), and diaphragmatic infarcts (clockwise rotation of loop in sagittal and frontal plane, the latter in the presence of a maximum QRS at +5°). Electrocardiogram shows left ventricular hypertrophy, suggests incomplete left bundle-branch block but does not indicate anteroseptal infarct. Since it is traditionally taught that in the presence of low QRS voltage in lead aV_F, a definite statement regarding diaphragmatic infarct is not warranted, this diagnosis could not be made either. Postmortem examination showed left ventricular hypertrophy and infarcts involving interventricular septum and diaphragmatic and apical surface of left ventricle.

Lateral Wall Infarction

Thirty-six cases were studied in this category (table 4). As in the previous group with anterolateral infarction, marked rightward displacement was observed for the initial vectors.[26] A division was made into 27 patients with counterclockwise rotation (fig. 7) and nine patients with clockwise rotation (fig. 9) of the initial part of the *horizontal plane* loop.

In those instances where counterclockwise rotation was observed, the 0.01-second vector was directed at 129°. This is significantly different from the normal (94°) ($p < 0.001$). This cannot be said for the direction of the 0.02-second vector as projected on this plane (81° vs. 84° in the normal). However, in 17 instances the loop made a sudden and abrupt rightward and posterior turn after the 0.02-second vector and continued with clockwise rotation into the left posterior quadrant (between 270° and 360°), as if the ventricular activation curve suddenly met an obstruction (figs. 7 and 8). Such "bites" have been described by Burch, using the tetrahedron,[12] by Portheine, using the Schellong reference system,[13] and by Howitt and Lawrie,[24] using the cube system. An explanation for this phenomenon may be offered along lines previously

Table 7

*Mean Values (in Degrees) of Selected Instantaneous Vectors in 51 Cases of Apical and 71 Cases of Diaphragmatic Infarction with Clockwise Rotation in Frontal Plane**

	Plane and rotation	No. cases Total	Autopsied	0.02 sec.	0.025 sec.	0.03 sec.	Maximum vector	No. of "bites"
Apical infarcts	Frontal clockwise	51	(7)	289 (271)	307 (300)	327 (323)	42 (38)	10
	Sagittal clockwise	14	(4)	263 (269)	294 (303)	324 (358)	6 (17)	2
	Sagittal counterclockwise	35	(3)	225 (262)	207 (257)	202 (251)	57 (84)	8
Diaphragmatic infarcts	Frontal clockwise	71	(5)	317 (314)	338 (328)	358 (342)	48 (25)	11
	Sagittal clockwise	37	(5)	290 (298)	309 (313)	339 (330)	28 (355)	4
	Sagittal counterclockwise	34	(0)	226 (—)	192 (—)	135 (—)	37 (—)	7

*Since these data are a composite of the subgroups described in tables 5 A, B, and C, tables 6 A, B, and C, and in the text, no S.D. or S.E. has been calculated.

discussed. At 0.025 second, when this abrupt reversal of direction is usually encountered, the endocardium and Purkinje system are usually fully depolarized.[20, 21-23, 27] The activation wave then advances more slowly toward the epicardium.[28] If this slower phase of activation, progressing as it were from cell to cell, meets an electrically inert area in the outer half of the free lateral wall, the remaining regions of the myocardium divert the resultant vector during that time.[29] This could result in the sudden reversal from counterclockwise to clockwise rotation; such rotation was observed in the terminal limb of the loop in all of our cases (figs. 7 and 8, see also fig. 14), and has never been encountered in any of the normal subjects studied by corrected lead systems.[10, 11, 31, 44]

Of the 9 cases with clockwise rotation, four were examined post mortem. Each of these showed very extensive infarction involving the entire free left ventricular wall, extending both anteriorly and posteriorly. Depending upon the degree of involvement, then, the loop may rotate in a clockwise direction from its very onset or at some time after initial normal activation. In the first instance the loop will be entirely clockwise (fig. 9), in the latter a "bite" will be inscribed (figs. 7 and 8).

In the patients showing the most extensive lateral wall infarction significant rightward displacement of the 0.03-second vector and of the maximum QRSsÊ vector was observed in the frontal plane. This occurred regardless of whether the loop rotated in a clockwise (five cases) or in a counterclockwise (four cases) direction (table 4B).

Thus either an abnormal rightward direction of the initial portion of the QRS loop in the horizontal plane or a "bite" in its middle portion is required for the vectorcardiographic diagnosis of lateral wall infarct.

It is significant that of the 36 cases, 19 showed associated infarction in the apical and diaphragmatic regions. As described by Portheine,[13] it was largely in this group that the high incidence of "bites" was noted. These may be transient (fig. 11). In none of the four autopsied cases with counterclockwise rotation in the sagittal plane was apical or diaphragmatic infarction noted. On the other hand, in each of the three non-autopsied cases (table 4C) with clockwise rotation, vectorcardiographic evidence for apical infarction was present. This re-emphasizes the importance of examining the direction of rotation in the sagittal plane to establish the presence or absence of associated diaphragmatic or apical infarction.

Apical and Diaphragmatic Infarction

There was considerable difference in the configuration of loops in both the frontal and the sagittal planes between cases with apical

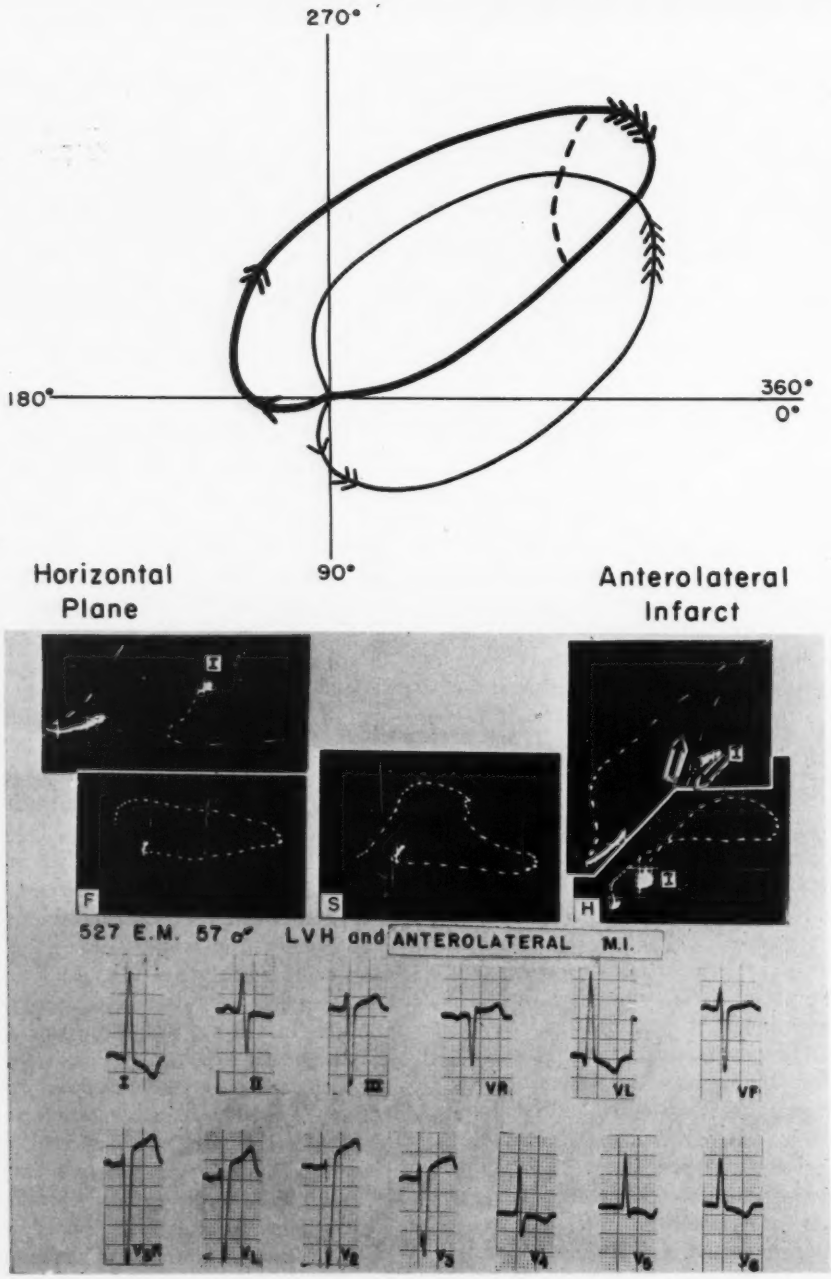

Figure 6

Anterolateral infarction. Diagram (upper) of horizontal plane QRSsÊ loop. Note clockwise rotation of loop and wide separation between 0.02-second vector with this type of infarction and that recorded in normal subjects. There is also displacement of the maximum QRS vector (cf. table 3). Demonstration of infarct (lower) in vectorcardiogram, not in electrocardiogram. The 0.01-second vector in the horizontal plane is at 145°, the 0.02-second vector at 270°. Clockwise rotation is present in the horizontal plane. Patient presented a classical clinical attack with elevated lactic acid dehydrogenase.

Table 10

Influence of Associated Infarction on Direction of Rotation in Sagittal Plane

Location of "primary" infarct	Total no.	No. rotating in normal (counterclockwise) direction	No. showing associated infarct	No. rotating in abnormal (clockwise) direction	No. showing associated infarct
Anteroseptal	44	30 (4)	1 (0)*	14 (3)	12 (3)*
Anterolateral	31	12 (2)	2 (0)*	19 (4)	15 (4)*
Apical	51	36 (3)†	6 (1)‡	15 (4)**	12 (4)‡
Diaphragmatic	71	34 (0)§	3 (0)‡	37 (5)	19 (5)‡

*Associated infarct was diaphragmatic or apical.

†Associated infarct was posterobasal in 25 (2).

‡Associated infarct was anteroseptal or anterolateral.

§Associated infarct was posterobasal in 25 (0).

**One showed posterobasal infarct.

The numbers in parentheses refer to cases that were studied at autopsy.

infarction and those with pure diaphragmatic infarction (tables 7A and B). The entire category of 124 cases with infarction in inferior areas of the heart was therefore subdivided according to the direction of rotation of the frontal plane loop and according to the position of the maximum QRS vector in the frontal plane. Thus, in contrast to the method used in the previous publication,[1] apical and diaphragmatic infarctions are here considered separately.

Apical Infarction

Of 53 patients, 51 displayed clockwise rotation in the *frontal plane* loop. These were subdivided into three groups: (1) a category in which the maximum QRS vector was in the range between 270° and 32° (proceeding clockwise) (fig. 10, table 5A); (2) a group with the maximum QRS vector between 52° and 141° (table 5B), and (3) a group with the maximum frontal plane QRS axis located within the range of normal (32° to 52°) (table 5C). In this *first* category (39 cases) superior displacement of the entire frontal plane QRSsÊ loop was the rule. Paralleling this was a significant superior displacement of the maximum QRS vector (mean value 5°, S.D. 18.5°) from the normal ($p < 0.001$). The corresponding measurement in the autopsied group was 13° (table 5A). The maximum QRS vector therefore serves as a reliable guide to loop displacement in this group.

The mean value of the 0.02-second vector for the autopsied cases (265°) appears to be representative for this entire subgroup (277°). These findings correspond to those of Pearce and Chapman[30] for the standard electrocardiogram. Also the 0.025-second vector (294°) and the 0.03-second vector (323°) showed pronounced superior deviation. All of these showed significant differences from the normal ($p < 0.001$).

Location of the maximum QRS vector in this range would ordinarily be associated with counterclockwise rotation of the entire loop.[10, 11] This was noted, for example, in all of our cases with left axis deviation due to left ventricular hypertrophy. Furthermore, in our normal controls the one case with the most extreme leftward displacement of the maximal QRS vector in the frontal plane, assuming clockwise rotation, showed a maximal QRS of 20°. Hence, the observation of *initial clockwise* rotation in association with the maximum QRS vector in the range between 270° and 20° in the frontal plane, in itself constitutes one of the most reliable signs of apical infarction (figs. 10 and 12). This also applies when the superiorly directed forces are of shorter duration than 0.0275 second. This phenomenon is readily apparent in the vectorcardiogram of figure 5, where the electrocardiogram does not justify this diagnosis.

Of this first group the *sagittal plane* loop (table 5A) displayed initial counterclockwise rotation in 28 of 38 cases (figs. 10, 11, and 13). The observed values demonstrated some overlap with those found in the normal. How-

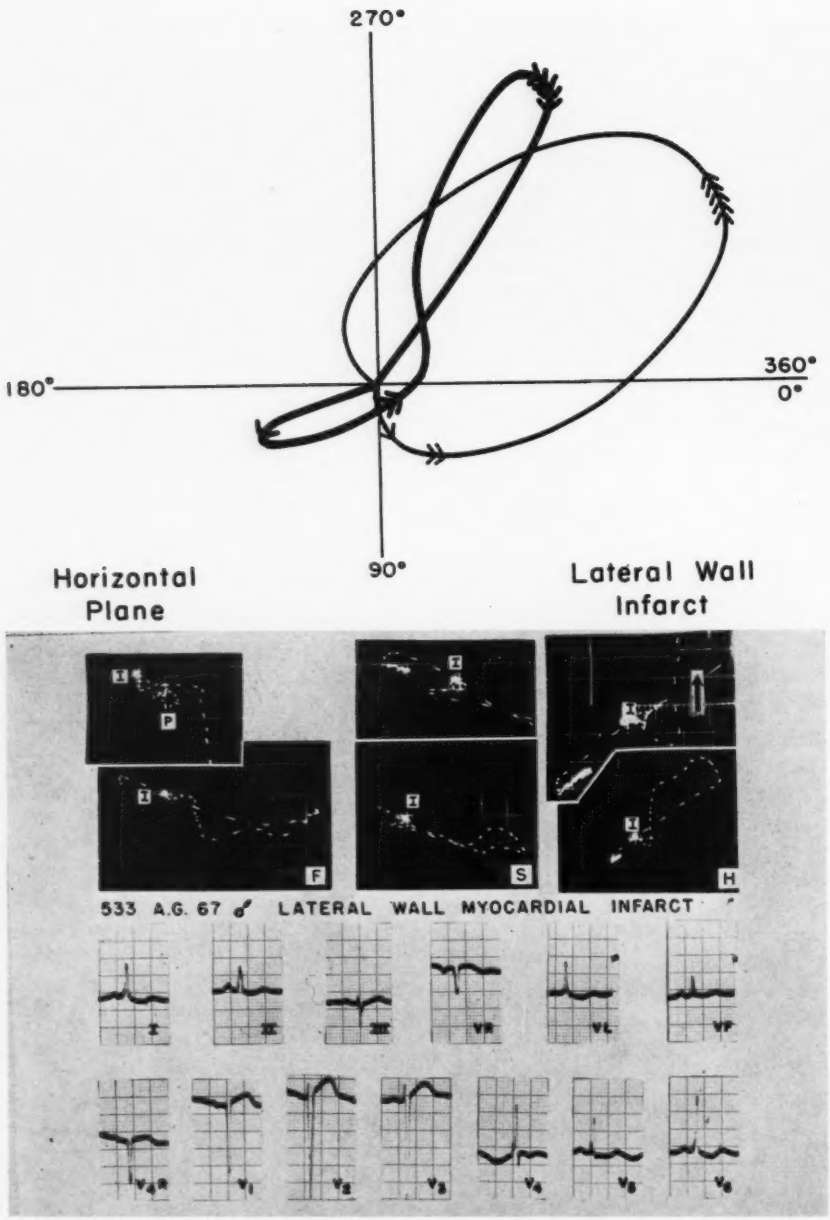

Figure 7

Lateral wall infarction. Diagram (upper) of horizontal plane QRSsÊ loop. The 0,01-second vector is displaced significantly to the right. The peripheral part of the loop is twisted into a figure-of-eight pattern ("bite"). Horizontal plane vectorcardiogram (lower) shows the latter, one of the characteristic changes of lateral infarct. This was confirmed at autopsy. The electrocardiogram failed to indicate the correct diagnosis. P refers to P loop.

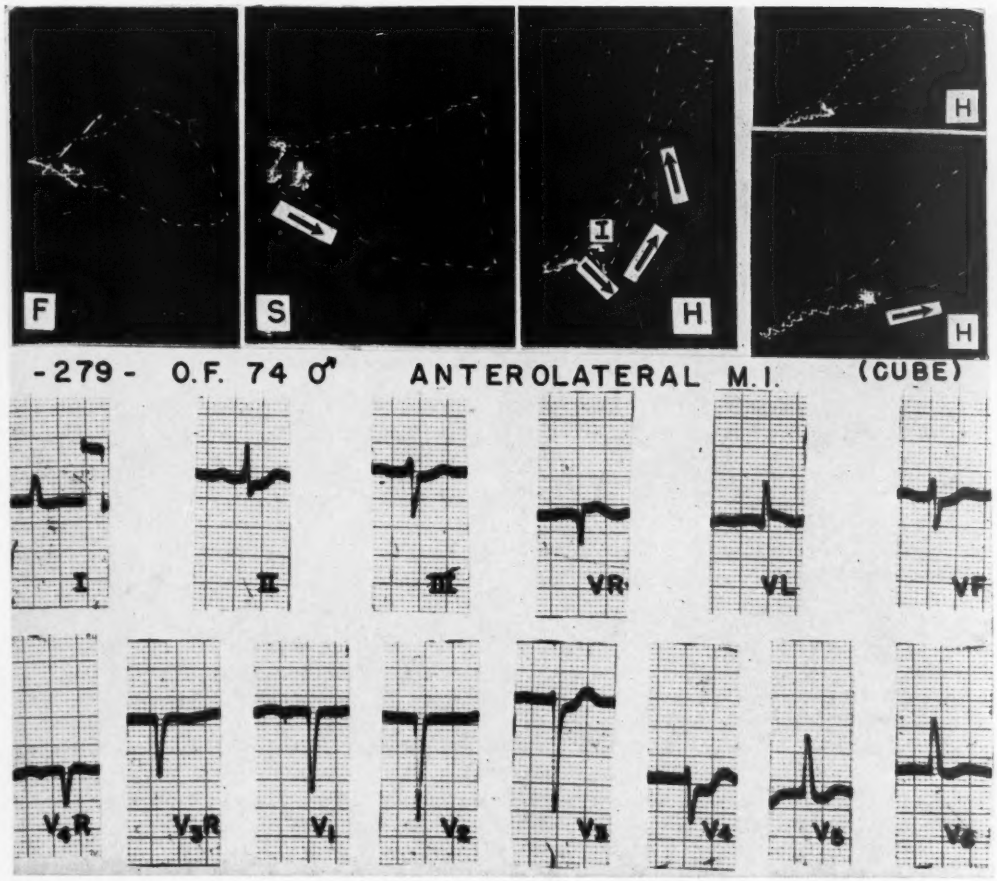

Figure 8

Difference between vectorcardiogram and electrocardiogram in localization of infarct. The Frank vectorcardiogram (third frame) locates the infarct in the anterolateral region (0.01-second vector at 73°, 0.02-second vector at 316); the electrocardiogram suggests an anteroseptal location. The cube technic also indicated that the infarct was anteroseptal (right-hand frames). At autopsy the infarct was in the anterolateral wall.

ever, in this group there was considerable individual variation and the two autopsied cases showed marked superior displacement well beyond the range of normal.

In the remaining 10 clockwise rotation was observed in the *sagittal plane* (figs. 5 and 10). In eight of these 10, additional evidence of either anterolateral or lateral wall involvement was present in the horizontal plane QRSsÊ loop (table 10). This corresponds with earlier observations made with the cube system.[1] Conversely, of the 28 cases with counterclockwise rotation in the sagittal plane only two demonstrated evidence of additional anterolateral infarction.

It is clear then that in this first category with superiorly displaced maximum QRSsÊ axis in the frontal plane the diagnosis of apical infarction can be made on the basis of the initial clockwise rotation alone. Furthermore, superiorly displaced initial vectors are the rule up to 0.03 second. In these cases ad-

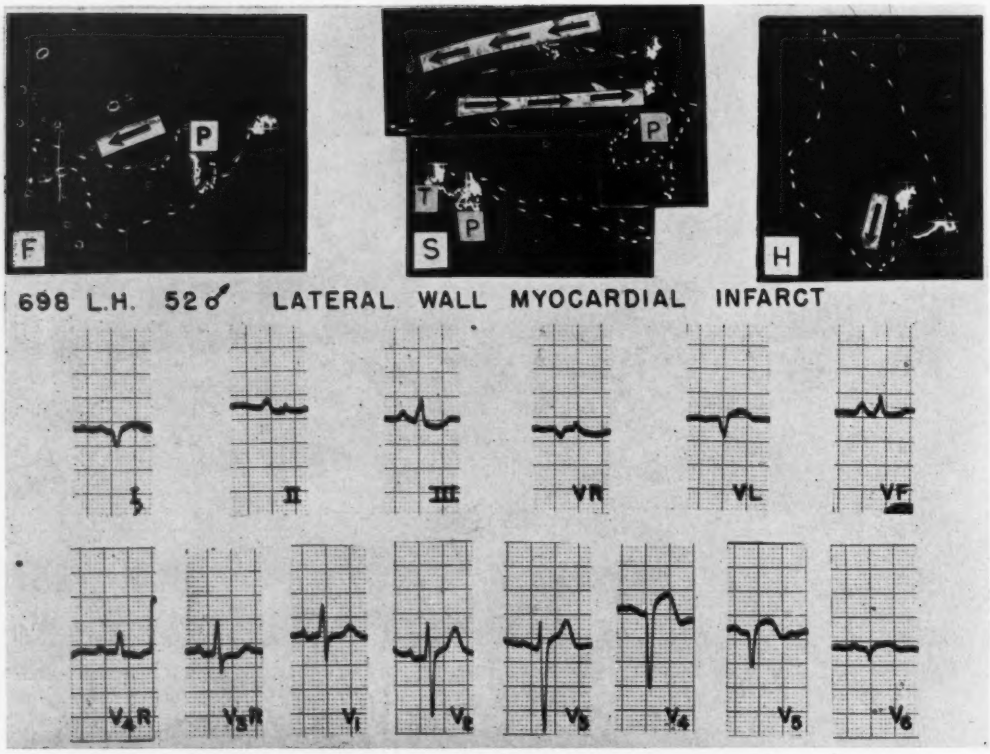

Figure 9

Vectorcardiogram and electrocardiogram in lateral wall infarct. The horizontal plane loop here shows clockwise rotation throughout its entire sweep. The 0.01-second vector is at 102°, 0.02-second vector at 103°, and 0.03-second vector at 111°; this indicates that the anteroseptal region is spared by the infarct. T loop absent in horizontal and frontal planes. The sagittal plane loop rotates counterclockwise in its initial segment. This is obscured by T loop in nonamplified lower frame but, with amplification and "dissection" of loop (upper frame), omitting the T loop, this salient is clearly demonstrated (arrows). The 0.02-second vector is at 160°, the 0.03-second vector at 149°. The frontal plane loop shows counterclockwise rotation. At autopsy the entire free left ventricular wall was infarcted.

ditional anterior myocardial infarction should be suspected if the sagittal plane loop rotates in an abnormal direction. This principle is well illustrated by figures 5 and 12 (table 10).

The remaining 14 patients fell into three small subgroups, none of which satisfied the complete criteria outlined above. The details of these categories follow:

In the *second* group with apical infarction (eight cases) (table 5B) the maximum frontal plane QRS vector was found in a range between 52° and 141°. In all, the loop rotated in clockwise direction, which is normal in this plane, when the maximum axis is in this range. The diagnosis, therefore, depended entirely on the duration of superiorly directed forces and their direction (fig. 11). Because of wide scatter, Pipberger[10] could give no quantitative data for the 0.01- and the 0.02-second vector in the frontal plane. However, comparison of the mean values for this second subgroup of cases with apical infarction with our own control observations and those of Mori[31] in a group of older men showed a significant superior displacement of the 0.02-second vector (292°) and of the 0.025-second vector (300°), (table 5B). The 0.03-second vector (338°) was also considerably displaced from the normal value of 28° ($p < 0.01$ in all).

Three of the eight cases showed counterclockwise

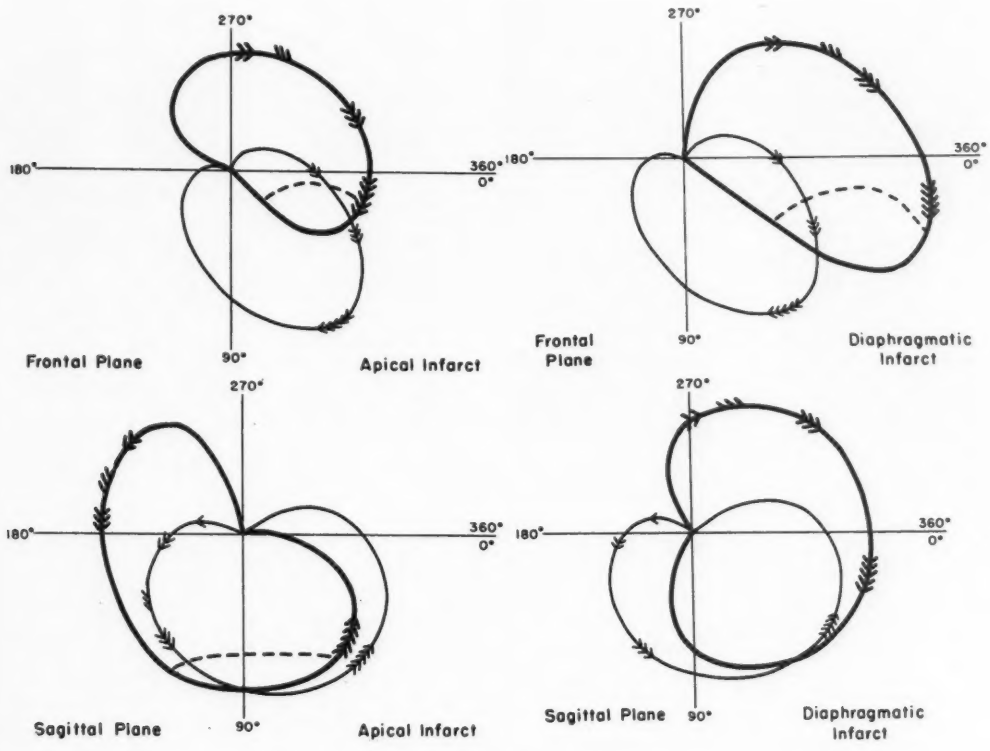

Figure 10

Diagram of frontal and sagittal plane QRSsÊ loops in apical and diaphragmatic infarction. (cf. table 7). In the left-hand pair of drawings (apical infarction) the maximum frontal plane *QRSsÊ vector, the vectors at 0.02, 0.025, and 0.03 second are significantly displaced superiorly as compared with the normal. The superimposed broken line depicts the "bite" in the peripheral part of the loop, not infrequently observed in these cases.* The sagittal plane *shows insignificant deviation of the 0.02-second vector from normal but superior displacement of the 0.025-second vector with counterclockwise rotation. This configuration could also be observed with diaphragmatic infarction. In the right-hand pair of drawings (diaphragmatic infarction) the maximum frontal plane QRSsÊ vector, and the vectors at the 0.02, 0.025, and 0.03 second are significantly displaced superiorly as compared with the normal. The sagittal plane shows similar displacement of the initial vectors. In contrast to the opposite figure (lower left) the loop here shows clockwise rotation. Such configuration may also be seen in apical infarction and implies concomitant anterior wall infarction (table 10).*

rotation in the *sagittal plane*. Although the early vectors demonstrated a considerable increase in the duration of superiorly directed forces (cf. tables 5B and 5A), only the 0.03-second vector differed significantly from the normal (219° vs. 138° for the normal).

In the remaining four cases in which sagittal plane observations were made, clockwise rotation was present. Three of these were examined post mortem. Two showed associated anterolateral infarction, while the remaining case demonstrated severe pericarditis and myocarditis, involving the anterior wall of the heart as well as the apical lesion. Thus, clockwise rotation in the sagittal plane appears to occur when the anterior wall as well as the apex is involved (table 10).

In the *third* subgroup with clockwise rotation in the frontal plane the maximum QRS was found

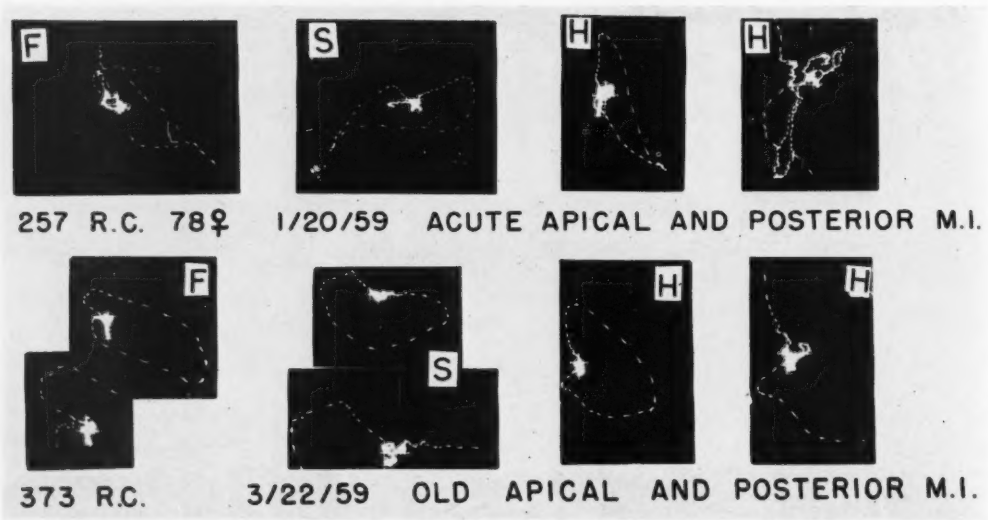

Figure 11

Apical infarction (VCG 257) manifested by (1) superior displacement of initial forces; (in the frontal plane the 0.02-second vector is at 257°, 0.025-second vector at 318°, and 0.03-second vector at 328°; clockwise rotation is present. In the sagittal plane the 0.02-second vector is at 202°, the 0.025-second vector at 193°, and the 0.03-second vector at 185°; counterclockwise rotation is present); and (2) by abrupt deviation of loop at 0.04 second ("bite"). The latter was a transient phenomenon, the vectorcardiogram 2 months later (VCG 373) showing similar abnormality of the initial forces with smoothing out of the remainder of the QRS loops. There is evidence of additional involvement of the posterobasal and posterolateral regions, best seen in amplified horizontal plane loop (right frame of each row).

in a normal range (32° to 52°, table 5C). Here again, there was marked superior displacement of the early vectors. As in the previous subgroup the 0.03-second vector in these four cases differed significantly from the normal (321° vs. 28°).

All four demonstrated counterclockwise rotation of the sagittal plane QRSsÉ loops. All of these had, by vectoreardiogram, associated posterobasal infarction. The values for the single autopsied case in this subgroup were in close agreement with the remaining cases. However, in all, these measurements differed very little from the normal.

A last category consists of two patients demonstrating counterclockwise rotation in the frontal plane; both showed abnormal upwardly directed forces. Additional lateral wall infarction was found in each at autopsy (table 5D, fig. 9). In the one patient who demonstrated clockwise rotation in the sagittal plane, the infarct extended into the anterior wall; in the other the rotation was in the expected normal counterclockwise direction and the additional infarct was confined to the lateral wall.

Diaphragmatic Infarction

As in the preceding section, a division into four subgroups was established. The *first* category consisted of 56 cases showing clockwise rotation in the frontal plane with a maximum QRS vector ranging between 262° and 32°. Three of these came to autopsy (table 6A, figs. 10 and 12). A close agreement was observed for both the autopsied and non-autopsied cases with regard to the 0.02-second vector (319° vs. 329°), the 0.025-second vector (334° vs. 345°), and the 0.03-second vector (346° vs. 360°). Since the very early vectors in this subgroup showed some overlap with normal measurements, clockwise rotation remained the most significant evidence for diaphragmatic infarction in this group, assuming a maximum QRS axis of 7° (± 20.2°). However, the 0.025- and the 0.03-second vectors

also proved to be significantly different from their normal counterparts ($p < 0.001$).

Thirty of these 56 demonstrated clockwise rotation in the sagittal plane as well (fig. 12). Again, considerable variation was found between individual values in this group, resulting in a large standard deviation (table 6A). All three autopsied cases showed clockwise rotation in this plane in addition to significant superior forces; therefore, a further diagnosis of anterior wall infarction was made. In each case this was confirmed at autopsy (figs. 5 and 12).

In the remaining 26, counterclockwise rotation was present in the sagittal plane (fig. 13). As in previous groups, the variation in individual measurements was wide, resulting in large standard deviations. Distinction from the normal was impossible in many instances.

In the *second* subgroup there were six cases (table 6B) (fig. 13). Here the maximum frontal QRS vector ranged between 52° and 142°. Clockwise rotation existed in all. The vectors at 0.02 second and 0.025 second showed significant superior displacement, when compared with the cases reported by Mori et al.[31] and with our normal controls.[11] However, this did not apply to the 0.03-second vector.

The observations in the *sagittal plane* of this group were divided into three cases with clockwise rotation (each of which showed associated anteroseptal or anterior wall infarct, confirmed in the autopsied patient) and three with counterclockwise rotation. The latter were as difficult to separate from normal controls as those presented in table 6A.

There were nine cases in the *third* subgroup of diaphragmatic infarction. All had their maximum QRSsÊ vector in the frontal plane within the normal range (32° to 52°, table 6C). Although the observed measurements for the 0.02-second vector (306°), the 0.025-second vector (334°), and the 0.03-second vector (355°) showed more superior displacement than those in group 6B, separation from normal controls remained difficult.

Finally, there remained a *fourth* subgroup of 10 cases with counterclockwise rotation of the frontal plane QRSsÊ loop (tables 6D and 6E). In eight the QRSsÊ loops were located in the right superior quadrant, with their maximum axis between 180° and 270°. All of them presented vectorcardiographic evidence of infarction in both the anterior and posterior walls. But since none of these was eventually examined post mortem, further discussion of these cases is omitted.

In summary, it appears that, if the maximal QRS vector lies above 20° in the *frontal plane*, initial clockwise rotation in this plane is one of the most reliable signs of diaphragmatic infarction (fig. 10). This was present in 56 of the 71 cases and in 94 of the total of 122 cases of both apical and diaphragmatic infarction (table 8). In no other condition, excepting the Wolff-Parkinson-White syndrome, has clockwise rotation been noted in association with such a pronounced degree of superior displacement of the maximum axis.

Finally, superior orientation of initial forces directly upward or leftward is the rule with diaphragmatic infarction. However, since there was some overlap with the normal in the direction of the 0.03-second vector, the instantaneous frontal plane 0.025-second vector was analyzed in more detail. In the data given for normal older men by Mori[31] and for younger individuals studied in this laboratory (0.025 second at 36°),[11] as well as for the more heterogeneous age group measured by Pipberger,[10] the normal extrapolated value for this instant lies below the 0° to 180° axis. By contrast, the 0.025-second vector invariably lies well above this axis (338° for the entire group of 71 patients, 326° for the five who came to autopsy) in patients with diaphragmatic infarction (table 7A). For the total group of 122 cases the direction of this vector was 317°, contrasting with a normal value of 36° ($p < 0.001$). Similar findings have been reported by Milnor and co-workers[32] and others.[24, 30] It is of interest that displacement of the same 0.025-second vector above the 0° to the 180° axis was also found to be the most reliable evidence for diaphragmatic or apical infarction with the cube technic.[1]

The sagittal plane showed counterclockwise rotation in 69 of 122 cases (fig. 10). For all initial vectors (table 8) studied there was some overlap with the normal, however, if the 0.025-second vector points above the 0° to 180° axis in this plane, apical or diaphragmatic infarction is probably present. The mean value for this vector in all 69 cases was

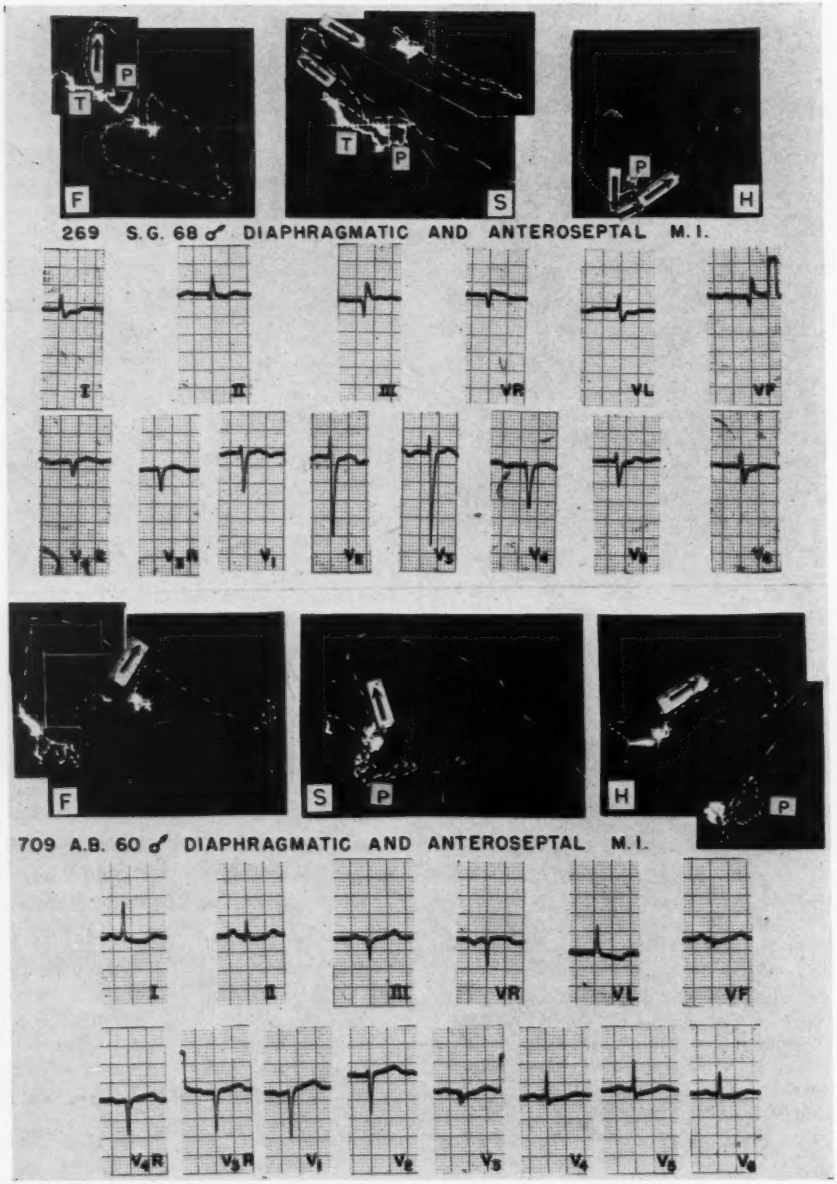

Figure 12

Two cases with diaphragmatic and anteroseptal infarction. In each case the former was demonstrated by prominent superiorly directed forces in the frontal and sagittal planes, the latter by clockwise rotation in the sagittal plane. The first case (VCG 269) differed from the second (VCG 709) in the presence of an initial early anterior vector (0.03-second). At first sight this suggested that the anteroseptal area was intact but the alternative explanation, that the persistent anterior force was the effect of an

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199°, contrasting with the normal value of 155° ($p < 0.001$). Clockwise rotation of the sagittal plane, with superior displacement of initial vectors, is abnormal in itself and constitutes reliable evidence for associated anterior wall infarction. This occurred in 52 of the total group of 122. In only 31 of these was there other vectorcardiographic evidence decisive for infarction of the anterior or anterolateral wall (table 10). Two additional cases had presented at some time in the past a classical electrocardiographic sequence for anteroseptal infarction, but at the time of this examination this was present in neither the electrocardiogram nor the vectorcardiogram by the standard criteria.

Peripheral loop "bites," similar to those discussed above, were observed in 11 of the 71 cases with diaphragmatic infarction (table 7A) and in 10 of the 51 cases with apical infarction (table 7B) (fig. 11).

Posterobasal Myocardial Infarction

Of the total 33 cases available for analysis, 29 demonstrated counterclockwise rotation in the horizontal plane loop (table 9). Each showed considerable anterior displacement of the initial part of the QRSsÊ loop (fig. 13, upper). As in the previous study[1] there appears to be little or no influence on the direction of the vectors at 0.01, 0.02, and 0.03) second in most cases with posterobasal infarcts. Similar statements have been made in the literature.[14, 33] If the infarct extends to the posterolateral region, however, the initial vectors are much more strikingly and distinctly displaced anteriorly[13] (figs. 11 and 13). Since the influence of an area of electrically inert myocardial tissue, ordinarily depolarized late in the QRS interval, should be reflected in the late vectors,[33, 34] it appeared worth while to study the 0.04-second as well as the maximum QRS vectors. The mean 0.04-second vector was located at 16° (normal 356°), a significant difference ($p < 0.05$), and the maximum QRS at 357° (normal 323°). Since subepicardial infarction of the posterior wall would tend to reduce the magnitude rather than change the direction of late QRS forces,[15, 33] an analysis of the area of the QRSsÊ loop anterior to the 0° to 180° axis may also prove worth while. This is one of the few circumstances encountered during this entire study in which measurement of the magnitude of the various instantaneous vectors might be more productive than the analysis of the direction alone.

In the remaining four cases with clockwise rotation in the horizontal plane (table 7) differentiation from right ventricular hypertrophy[13] proved very difficult. This is discussed in greater detail later.

Discussion

Electrocardiographic Observations vs. Vectorcardiographic Data

It has long been recognized that the electrocardiographic diagnosis of myocardial infarction, particularly old infarction, is subject to considerable error. Katz,[35] Johnson,[36] Gray,[37] Paton,[38] and others[39, 40] have estimated the percentage of error to be between 20 and 75 per cent. It is known also that a diagnostic electrocardiographic abnormality, present at one time, may disappear partially or completely for a variable period of time, frequently to return at a later date. Patients with well-established inferior myocardial infarction, for example, may lose the diagnostic evidence of their infarct because of a decrease in depth and duration of the Q waves in leads III and aV_F[34] (fig. 14). Similarly, patients with old anteroseptal infarction may show a waxing and waning in the voltage of the precordial R waves so that at one time the tracings are and, at other times, are not

additional posterobasal infarct, was borne out at autopsy. In the second case the 0.02-second vector in the horizontal plane is directed at 323°, hence the diaphragmatic infarct is complicated only by anteroseptal involvement. In the first case these electrical events are present in the electrocardiogram but are perhaps more clearly depicted in the vectorcardiogram. In the second case, although anteroseptal infarct is suggested by a decreasing R from lead V_2 to V_3, there is such low voltage in lead aV_F that an unequivocal diagnosis of diaphragmatic infarct was not justifiable.

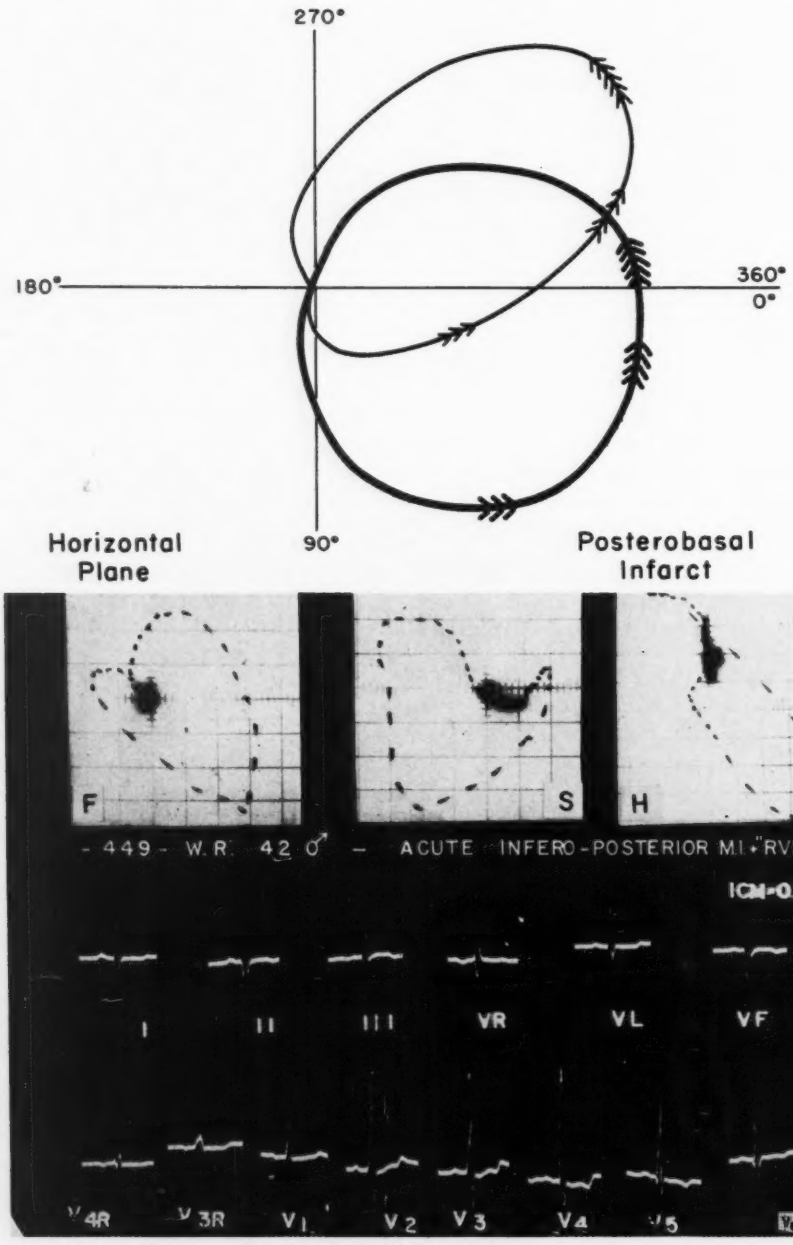

Figure 13

Posterobasal infarction. Upper diagram shows horizontal plane QRSsÊ loop. The large anterior salience is important in the diagnosis, since the vectors at 0.01, 0.02, and even 0.03 second do not differ significantly in location from corresponding instants in the normal vector loop. Vectorcardiogram shows large superior forces in frontal (0.025-

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characteristic of infarction. If in such instances of known previous infarction some method were available that permanently retained the diagnostic evidence for infarction, one could not help concluding that such a method possessed greater accuracy than the currently available electrocardiogram.

Of the 125 cases falling in groups A and B, all with convincing vectorcardiographic and clinical evidence for myocardial infarction, only 76 in electrocardiograms taken immediately after the vectorcardiogram demonstrated definite evidence of infarction according to the criteria enumerated above. In 18 of the remaining 49 cases (table 11) the electrocardiogram demonstrated infarct in only one area with certainty, whereas the vectorcardiogram indicated infarction of multiple and frequently contiguous areas. In an additional 20, the electrocardiographic evidence for infarction could be regarded as only questionable. The remaining 11 satisfied none of the diagnostic electrocardiographic criteria for infarction (9.6 per cent) (figs. 4, 5, 6, 7, and 12). It is to be emphasized that this series is weighted in favor of the electrocardiogram, since in all cases it had been diagnostic for infarction some time in the past; it was this very fact that led to their inclusion in the present study.

When this material was studied from the opposite point of view, that is, from the standpoint of the vectorcardiographic findings in patients who at one time or another had shown diagnostic electrocardiograms,[1] it was found that all such patients exhibited vectorcardiographic evidence of these infarcts at the present time. Furthermore, there were several instances, not included in this analysis of 125 cases, in which electrocardiograms had been interpreted as diagnostic of infarction; each of these patients showed no infarction in the vectorcardiogram and had no infarction at postmortem examination.

A discrepancy between the conventional 12-lead electrocardiogram and the vectorcardiogram as derived by the Frank lead system, is not unexpected in the light of the observations of Frank,[6] Langner,[4] and Pipberger.[5, 7] Among other factors such differences have been attributed to the inconstancy of the direction and magnitude of conventional effective lead axes, and to variations in the dipole position and in body build. A number of systems, including that of Frank, have been designed to correct these errors and have resulted in a narrower range of normal values, less overlap between normal and pathologic measurements, and improved reproducibility of the loops from time to time (fig. 14). Although in isolated instances comparisons were made between the loops recorded with the cube and with the Frank system (figs. 2 and 8), a wholesale confrontation of the two technics was not attempted.

Of the 24 cases examined at autopsy (group A) it was possible accurately to predict the area of infarction from the vectorcardiogram in 21 cases. In the remaining three, vectorcardiographic localization was inaccurate. In two of these, widespread infarction was found; presumably as a consequence of this the resultant vector incriminated an area in which no infarct was found. In the third case the reason for the inaccuracy is uncertain; it may be explained by a peculiar rotation of

second vector at 293°, 0.03-second vector at 308°), and sagittal (0.025-second vector at 221°, 0.03-second vector at 204°) planes establishing presence of diaphragmatic infarct. The horizontal plane shows counterclockwise rotation and preponderance of anterior forces, lasting 0.065 second, with initial rightward component (0.02-second vector at 120°, 0.04-second vector at 54°), indicating posterobasal and posterolateral involvement. This is borne out in the sagittal plane where the loop rotates counterclockwise with 80 per cent of the area of the loop anterior to the null-point. Such rotation in the sagittal plane with marked anterior displacement has been the rule in uncomplicated posterobasal infarction (cf. fig. 11). The electrocardiogram is clearly diagnostic of diaphragmatic infarction; the tall R waves in leads V_{4R}, V_{3R}, and particularly V_1 could be confused with right ventricular hypertrophy, but posterobasal infarction can be inferred from this change in the presence of diaphragmatic infarction.

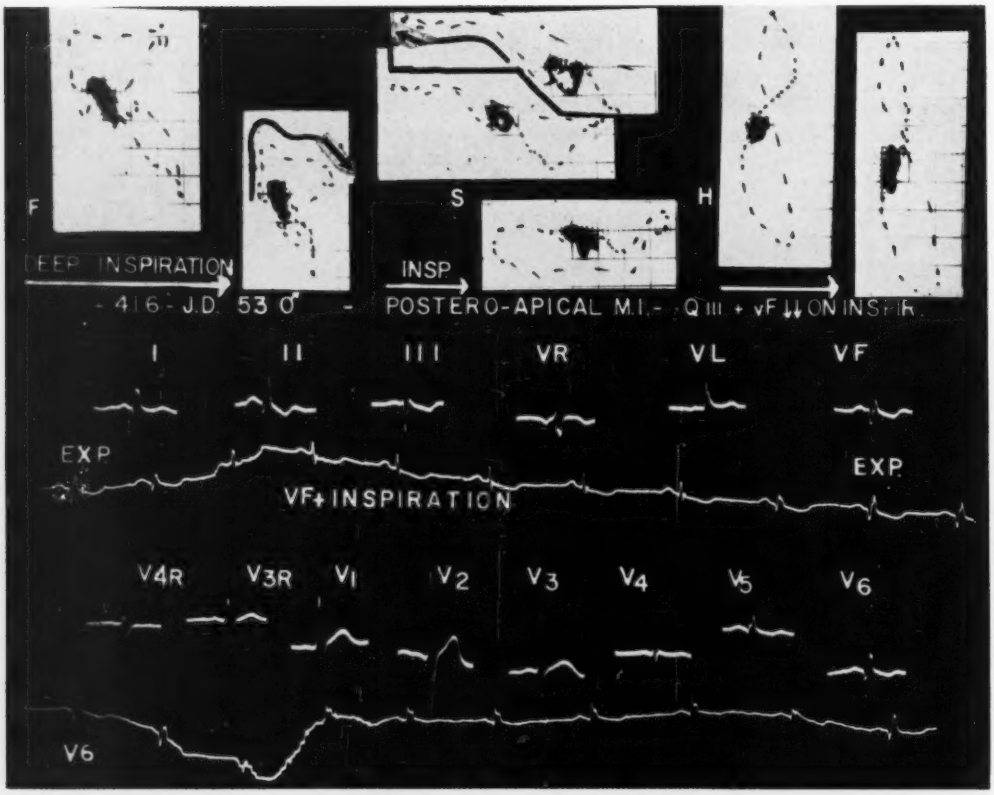

Figure 14

Effect of inspiration on vectorcardiographic and electrocardiographic (V_F, middle continuous line; V_6, lower continuous line) evidence of infarction involving apical, posterobasal, and posterolateral region of the heart. In the vectorcardiogram the large superior and anterior forces persist in the frontal and horizontal planes on inspiration, although the projection of these abnormal forces on the sagittal plane is so altered, that they approach variation of normal. This could be demonstrated repeatedly. By contrast the broad prominent Q wave in leads III (not shown in picture), V_F, and V_6 is replaced by an R wave on inspiration. This observation of a persistent superior vector in the frontal plane vectorcardiogram contrasting with the disappearance of the Q wave in aV_F on inspiration is in accordance with the predicted performance of the Frank lead system. Posterobasal infarction is indicated by the large anterior counterclockwise force in the horizontal and sagittal planes. The "bite," beginning at 0.0275 second in the frontal and horizontal planes, signals posterolateral involvement. In the electrocardiogram the tall R wave over the right precordium might be attributed to counterclockwise rotation of the heart on its longitudinal axis, but such an interpretation is not justified in the vectorcardiogram.

the heart and chamber hypertrophy. An apical infarct was diagnosed; a posterobasal infarct was found. It is apparent, then, that the same cancellation factors, which can affect the accuracy of the electrocardiogram may have a similar effect on the vectorcardiogram.

Pitfalls in Vectorcardiographic Diagnosis

On occasion the vectorcardiographic appearance of myocardial infarction may be simulated by other conditions. These are left bundle-branch block, which may be confused with anterolateral infarction, right ventricu-

lar hypertrophy, which may mimic posterobasal infarction, septal hypertrophy (as part of left ventricular hypertrophy), which may be mistaken for lateral wall infarction, and "giant right atrium,"[41] which may produce changes resembling anteroseptal infarction.

The differentiation between left bundle-branch block and anterolateral infarct has been discussed in the previous communication[1] dealing with the cube system. Since left bundle-branch block is regarded as only an electrocardiographic diagnosis[40] and since anatomic evidence for this lesion is frequently not forthcoming, it would appear to be futile to belabor the method of differentiating the two conditions. Furthermore, none of the patients in this series with left bundle-branch block by vectorcardiogram was subjected to postmortem examination. Suffice it to say, all but two of the 14 individuals whose electrocardiogram showed left bundle-branch block demonstrated an initial anterior force by vectorcardiogram as discussed by Frimpter et al.[42] It is in these patients, lacking the characteristic anterior part of the loop, in whom the diagnosis of anterolateral infarct may be considered. This differentiation was possible in a case recently studied by the injection-dissection technic, where the electrocardiographic finding of left bundle-branch block obscured the existence of myocardial infarction[43] but where the vectorcardiogram led to the correct diagnosis.

There is no real problem in differentiating between right ventricular hypertrophy on the one hand and posterobasal infarction on the other, when there is already convincing evidence of diaphragmatic or apical myocardial infarction in the frontal and sagittal planes. The problem may be more difficult when there is no associated diaphragmatic infarction. A distinguishing point may be the direction of rotation of the horizontal plane QRSsÊ loop.[19] In 29 of 33 cases of posterobasal infarction counterclockwise rotation was found. We have not observed this direction of rotation in adults with right ventricular hypertrophy, if there is a similar degree of anterior displacement of the loop. Furthermore, in none of the patients with this so-called "pseudo right ventricular hypertrophy" (figs. 13 and 14) was the maximum QRS vector in the frontal plane deviated to the right of 50°, as it is in true right ventricular hypertrophy.[19] It seems possible that there may be a rare case of mild right ventricular hypertrophy in which the horizontal plane QRSsÊ loop rotates entirely in a counterclockwise direction, but here the problem of differentiation from posterobasal infarction hardly arises, for there is no comparable degree of anterior salience of the loop.

Twenty-seven patients were observed who displayed a large initial rightward force in the frontal and horizontal plane suggesting lateral wall infarction (table 4). All fell in group B excepting a 32-year-old woman in whom there was considerable doubt that she had actually sustained a myocardial infarction. She had a massive heart, a blood pressure of 180/40, and severe free aortic regurgitation. From the discussion in the previous communication[1] it was concluded that in isolated instances pronounced septal hypertrophy (as seen in one autopsied case) may simulate lateral wall infarction. It appears that the patient under discussion belongs in this category.

In three other patients, each a young woman in the thirties, the vectorcardiogram and the electrocardiogram were interpreted as showing anterior wall infarction (fig. 15). In two of these patients postmortem examination showed a giant right atrium associated with an atrial septal defect of the secundum variety; roentgen-ray examination showed rotation of the heart, so that the bulk of the right ventricle was situated anteriorly. At autopsy there was no evidence of myocardial infarction. The electrocardiogram in all three patients resembled the pattern described by Sodi-Pallares.[41] Rheumatic heart disease with severe right-sided hypertrophy and dilatation, or congenital heart disease with similar changes, may induce QS or QR complexes over the right precordium. These are explained as ventricular cavity potentials transmitted through a giant right atrium or as the effect of a shift of the ventricular mass to the left, displacing the entire QRS field left-

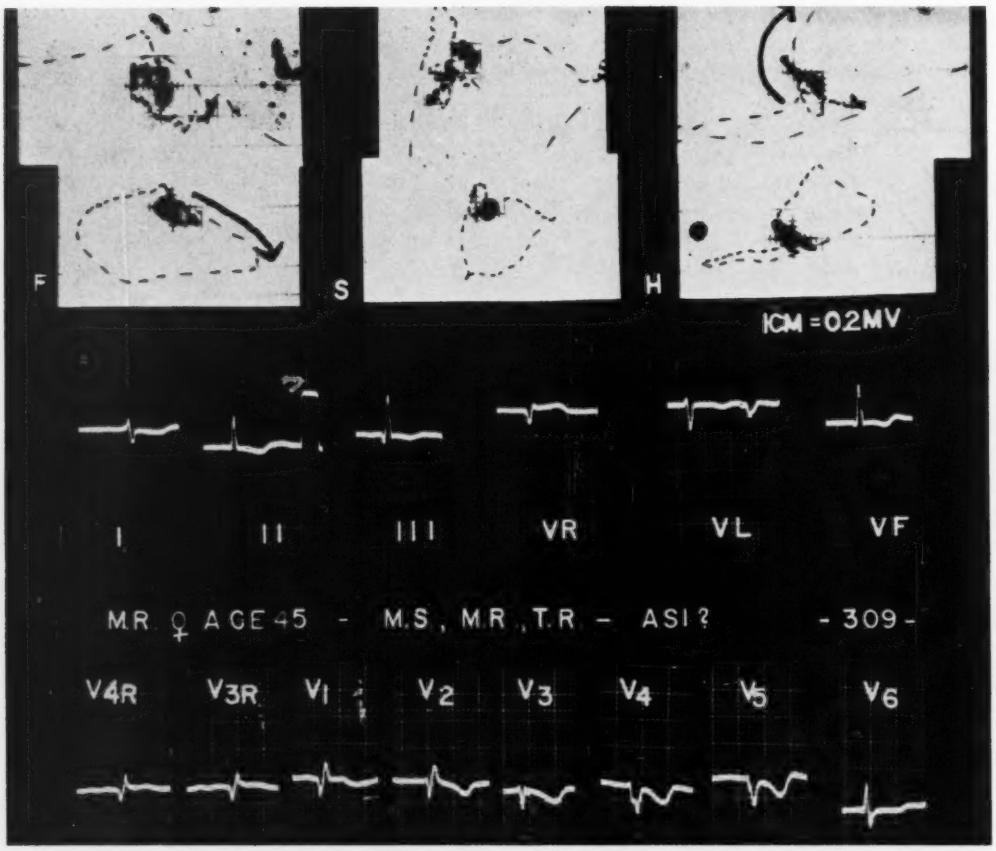

Figure 15

Electrocardiogram and vectorcardiogram in "giant right atrium." The electrocardiogram of this 45-year-old woman with severe rheumatic heart disease suggests extensive anterior wall infarction. Anterolateral infarct seems to be indicated by clockwise rotation of the horizontal plane loop with the 0.02-second vector at 180° and clockwise rotation in the sagittal plane. However, the presence of a maximum QRS vector in the frontal plane at 120° with clockwise rotation in the plane nullifies the significance of these findings, since with the suspected degree of anterolateral wall infarction, counterclockwise rotation would be expected in the frontal plane (cf. fig. 9). At autopsy no infarction was found.

ward and bringing normal initial negativity toward the center of the chest wall. The abnormal vectorcardiogram in our cases can be explained similarly.

This study was undertaken primarily to establish quantitative criteria for the vectorcardiographic diagnosis of myocardial infarction. Such quantitative data based upon objective measurements, expressed in degrees rather than upon qualitative terminology alone, have not yet been available. It demonstrates that, for the most part, measurements made in patients with infarction fall into discrete and statistically significant groups. It is recognized that the approach in this study had to be peripheral and exploratory. Consequently, it does not forge the final link establishing these criteria as unequivocally valid. In certain instances this method has given decisive information not present in the

electrocardiogram but the study does not prove beyond doubt the invariable superiority of the "modern" vectorcardiogram over the "traditional" electrocardiogram. The number of autopsied cases studied was too limited to justify such a conclusion. Judgment awaits the accumulation and publication of larger scale postmortem material. Such studies are now underway here and elsewhere.

Summary

Two-hundred six patients with myocardial infarction were studied with the Frank vectorcardiographic lead system and the standard 12-lead electrocardiogram in common use. Distinctive and statistically significant measurements separated these individuals from normal controls similarly studied.

Of 125 patients with convincing evidence of past myocardial infarction all showed abnormal vectorcardiograms. Only 76 of these presented electrocardiograms diagnostic of infarction at the time of the diagnostic vectorcardiogram. Eleven (9.6 per cent) showed no evidence of infarction in their electrocardiographic tracings.

The theory is held by some that modern vectorcardiography should be superior to conventional electrocardiography. The present observations in suspected myocardial infarction suggest that this method may yield confirmatory evidence in most cases, additional and complementary data in some, and decisive information not otherwise available, in a few.

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CLINICAL PROGRESS

The Use of Cinefluorography in Acquired Heart Disease

By JOSEPH JORGENS, M.D., PH.D., AND ARTHUR LIEBER, M.D.

CINEFLUOROGRAPHY, the process of taking motion pictures of the fluoroscopic screen of the image amplifier, is now the best method for detecting and recording calcifications and pulsations of the heart and will soon enjoy similar acceptance in angiocardiography.[1] Our purpose here is to describe this method, its clinical usefulness, and its limitations.

Equipment

The cinefluorograph is a standard fluoroscopic unit combined with an image amplifier tube and a motion picture camera. The amplifying tube produces a bright fluoroscopic image that can be photographed on motion picture film.

Several types of cinefluorographic units are commercially available.[2] When selecting a cinefluorograph, one should consider the importance of picture detail. Good detail can be obtained on a 5-inch image amplifier equipped with a 16-mm. camera. The 8- and 9-inch units recording on 16-mm. film do not seem to have as good detail as the 5-inch unit. This limitation can be corrected by changing to a camera lens of different focal length to magnify the image on the 16-mm. film frame (overframing) or by using 35-mm. film. The cinefluorograph may be combined with a television monitor so that several doctors may view the image simultaneously. For the best detail, however, the camera should record the amplifier's image rather than the image of the television monitor.

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In the examination of children, the larger field cinefluorograph is used for forward cineangiocardiography while the smaller 5-inch unit is restricted to routine cardiac cinefluorography and selective cineangiocardiography.

The amplification factor of the image is also important. If it is a high value (between 700 and 1,000 in the Westinghouse scale of brightness) the radiation dose necessary to produce a high quality film is less.

Either 16- or 35-mm. film may be used. Although more detail is present on the 35-mm. film, the equipment needed to develop and project the film is extremely costly. For this reason, 16-mm. film is more practical for routine use in most hospitals. Packaged in 100-foot rolls, the 16-mm. Kodak Linagraph Shellburst film can be developed in the standard x-ray darkroom with ordinary radiographic developing and fixing solutions. Usually 30 feet of film per cardiac examination at the rate of 15 frames per second will be sufficient.

Radiation Dosage

The amount of radiation dosage varies with the size of the heart and the density and thickness of the patient's tissue. At 110 kilovoltage the milliamperage fluctuates between 5 and 15 milliamperes for an average patient, resulting in a total radiation exposure of about 20 roentgens in air. This dose is delivered to a constantly changing skin field through a portal 4 3/4 inches in diameter. Because radiation should be limited sharply in young individuals, careful scrutiny with the use of the image amplifier only, will reveal abnormal pulsations of the heart border.

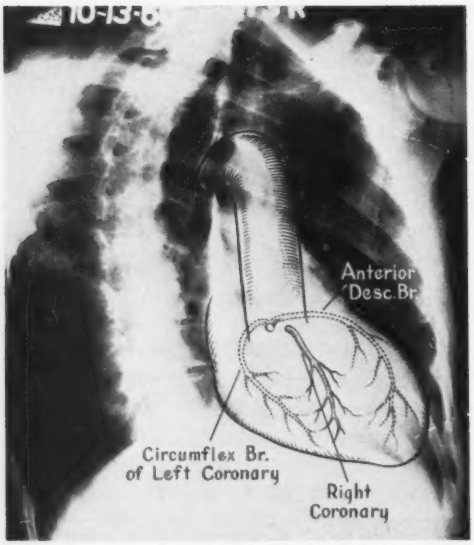

Figure 1

Right anterior oblique view showing position of the coronary arteries.

Only the mid-cardiac mass need be cinefluorographed for calcifications. This selectivity of filming results in very low radiation dosage.

Technic at Examination

Our cinefluorographic technic for examining the heart for calcifications and pulsations is as follows: 1. In the posteroanterior view the pulsations of the right cardiac border and the great vessels are recorded beginning at the diaphragm and moving upward to include the superior vena cava and azygos vein. In this film sequence, the pulsations of the right border of the heart and calcifications in the pericardium, right coronary artery, and ascending aorta can be noted. 2. In this same view the pulsations of the left border of the heart from the left subclavian artery down to the left hemidiaphragm are filmed. The characteristic pulsations of aortic insufficiency, fibrillation of the left atrial appendage, and the paradoxical pulsations of an aneurysm of the left ventricle may be shown. In this same sequence, calcifications in the arch of the aorta, pulmonary artery, left coronary artery, and myocardium of the left ventricle are revealed. 3. In the right anterior oblique position, a recording from the diaphragm to the pulmonary artery and thence down the left heart border to the diaphragm shows calcifications in the mitral and aortic valves and in right and left coronary arteries (fig. 1). 4. In the left anterior oblique projection, the pulsations of the right atrium and ascending aorta are recorded followed by a sequence through the mid-cardiac silhouette, including the right coronary artery, aortic valve, and left coronary artery. 5. In this same position, the pulsation of the posterior border of the heart is recorded. This view also includes the mitral valve area. 6. Finally, in the right lateral projection, beginning in the inferoposterior part of the cardiac silhouette, a sequence is obtained that crosses the mitral and aortic area to the retrosternal area of the heart. This view is best for the observance of the movement of the calcified leaflets of the aortic valve. Occasionally, a calcified right coronary artery may be seen in the anterior half of the heart, a calcified anterior descending or circumflex coronary branch in the superior half of the heart, and a calcified mitral valve in the inferoposterior portion of the heart.

Identification of Intracardiac Calcifications

In order to detect and to locate accurately small intracardiac calcifications, a definite sequence of cinefluorography including all the cardiac positions outlined previously should be used. For example, in the left anterior oblique projection a small fleck of calcium in the anterior descending branch of the left coronary artery might easily be mistaken for a fleck of calcium in the aortic valve. In the right anterior oblique view, however, this coronary calcification will be projected out near the left heart border, the characteristic position of the anterior descending branch of the left coronary artery (fig. 2).

In addition to location, other important factors aiding in the detection and localization of intracardiac calcifications are the movement and form of these calcium deposits. For example, calcified coronary arteries appear as

linear and curved calcifications that pulsate in unison with the heart and aortic borders. These may be differentiated from pericardial calcifications in that these pericardial calcifications run parallel to the heart surface in at least one view and move only slightly with the heart border. Calcified heart valves on the other hand may have a structureless appearance. The calcium often is clumped and not linear in appearance. The annuli of the aortic and mitral valves may cause considerable difficulty if only slightly calcified. If well calcified, then their location, "U" shape, and reduced movement will help in identification.

Calcification within the cardiac silhouette can be localized in still another way. Considerable fat is present in the atrioventricular groove of the heart. On the cinefluorogram in the left anterior oblique view, this fat appears as a radiolucent, pulsating line between the right atrium and right ventricle. The main right coronary artery is located in this black line. Flecks of calcium seen here are thus identified as flecks within the right coronary artery. Similarly in the right anterior oblique view the circumflex branch is seen in the fat deposited in the posterior portion of the atrioventricular groove, and the anterior descending branch in the fat deposited between the right ventricle and the left ventricle. In the lateral view, the anterior border of the aorta can often be located by the adjacent fat deposit. This identifying deposit can aid in identifying calcification of the aortic valve leaflet.

There are many factors aside from the small size of the intracardiac calcifications that may interfere with the detection of these calcium deposits by cinefluorography; these are obesity, cardiomegaly, pulmonary congestion and effusion, pulmonary and pleural disease of noncardiac origin, failure to examine the heart in all positions, and inattentiveness or inexperience of the observer.

Coronary Artery Calcification

The significance of calcification in the aortic or mitral valve is well known. On the other hand, the significance of coronary artery calcification[3, 4] is not widely known. The correlation of coronary artery calcification with clinical arteriosclerotic heart disease has recently been investigated with cinefluorography of the heart to detect and evaluate the coronary calcifications.[5] Previous radiologic studies, without the aid of cinefluorography, have been unable to confirm such correlation.

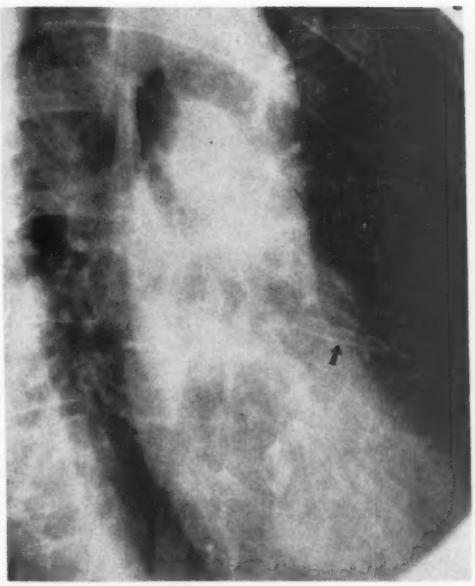

Figure 2

Right anterior oblique view showing a heavily calcified anterior descending branch of the left coronary artery (arrow).

In our study of 60 men, 15 in each decade from ages 40 to 80, with normal hearts as far as could be determined by history, physical examination, electrocardiogram, and chest film, 25 per cent were found to have coronary calcification at cinefluorography. The peak incidence was in the 60- to 69-year group.

In another group consisting of 630 consecutive cardiac cinefluorographies on men mainly between ages 40 and 70 with various types of known or suspected heart disease, 150 (23.8 per cent) had coronary calcification. Of the 150 patients with coronary calcification 58 per cent had arteriosclerotic heart disease by clinical evaluation as compared with 39 per

Figure 3

Posteroanterior view showing an increased distance between the subepicardial fat line (dotted line) and the cardiac outline due to a pericardial effusion (between arrows).

cent of a comparable group without coronary calcification at cinefluorography.

There was a further direct relation between the number of major coronary branches calcified at cinefluorography and the incidence of clinically manifested arteriosclerotic heart disease. In the 150 patients with coronary artery calcifications mentioned above, the majority of whom were between 40 and 70 years, the incidence of ischemic heart disease increased from 52 per cent in those with one major coronary artery calcified to 83 per cent in those with three major branches calcified.

As part of this investigation 21 autopsy protocols of patients with cardiac cinefluorographies were reviewed. Of 15 patients with coronary calcification at cinefluorography, 13 had moderate to heavy atherosclerosis of the coronary arteries at postmortem examination. Ten also had cardiac enlargement of various degrees that, however, did not seem to interfere with the detection of coronary calcification at cinefluorography.

Our conclusions were as follows: 1. Careful cinefluorography of the heart detects a high number of coronary artery calcifications. 2. Autopsies show that the presence of coronary calcification on cinefluorography indicates considerable coronary atherosclerosis. 3. There is a much higher incidence of angina and myocardial infarction in men when coronary calcification is detected at cinefluorography. 4. There appears to be a high correlation between coronary calcification at cinefluorography and clinically manifested arteriosclerotic heart disease if heart disease is evident or suspected. The cinefluorographic evidence of coronary calcification by itself, however, is unreliable in predicting the presence of symptomatic ischemic heart disease.

Since coronary arteriography at present is still unsuitable for routine use[6] due to the complexity of the equipment and the hazard to the patient, the detection of coronary calcification by the relatively simple, rapid, and innocuous method of cinefluorography may be the most efficient screening procedure for the detection of potential arteriosclerotic heart disease at a time when no electrocardiographic changes or signs and symptoms are present to indicate the extent of coronary atherosclerosis.

Cardiac Fat Lines

Cinefluorography lends itself very readily to the study of pulsating fat lines about the heart.[7] These fat lines appear as thin, radiolucent lines representing subepicardial fat. By the study of these fat lines the enlarged cardiac silhouette resulting from pericardial effusion can now be distinguished from that caused by myocardial dilatation.

Normally the fat line is only 2 mm. from the left lateral border of the heart. It is difficult to see, and it pulsates with the same ampli-

tude as the heart border. In the presence of pericardial effusion the distance between the fat line and the cardiac outline is increased (fig. 3). In addition, the fat line is relatively easy to detect and shows a more vigorous pulsation than the margin of the cardiac outline. In the presence of myocardial dilatation the distance between the fat line and the cardiac outline is normal. The fat line is difficult to define and shows a decreased amplitude of pulsation comparable to the decreased heart border movement.

Pulsations of the Heart and Great Vessels

Cinefluorography is the best method for recording pulsations. Pulsations, moving at right angles to each other, can be recorded simultaneously. The duration of recording is not limited as in roentgenkymography.[8] As yet, the electrokymograph is an experimental tool. Eventually, it should prove valuable for quantitating the amplitude of pulsations of the heart and great vessels.[9, 10]

Pulsations of the various chambers and vessels of the heart are useful in the radiographic diagnosis of heart disease. For instance, when the heart is normal in size and shape in a patient with early aortic insufficiency, it can only be recognized radiographically by the presence of an increased amplitude of pulsation of the aorta.

The paradoxical pulsation of the left heart border associated with a ventricular aneurysm, the decreased amplitude of pulsation associated with a pericardial effusion or myocardial insufficiency, and the increased amplitude of pulsation associated with bradycardia, all are findings that may be valuable in the final radiographic diagnosis.

Adhesions of the Pleuropericardium

Cinefluorography is also the best method for recording adhesions of the pleuropericardium. Adhesions about the heart have been neglected as a finding in radiographic diagnosis. In a preliminary survey of 120 Veterans Administration Hospital patients with cinefluorographic evidence of pleuropericardial adhesions, 38 per cent had a discharge diagnosis or manifestation of arteriosclerotic heart disease. Of 50 patients with both coronary calcifications and pleuropericardial adhesions, 48 per cent had findings of arteriosclerotic heart disease.

Angiocardiography

The use of cinefluorography for forward angiocardiography is still not accepted by most cardioroentgenologists. They hold that the detail of the roentgenogram and the convenience of studying standard films outweigh the advantage of visualizing the contrast agent moving through the different chambers and vessels of the heart. Only for selective angiocardiography in children is the small 5-inch cinefluorograph diagnostically feasible. Eventually a large 2-plane cinefluorograph will replace the rapid cassette changers of today.

Disadvantages

There are several minor disadvantages inherent in the cinefluorographic method. When using a small-field image amplifier, inexperienced doctors may find it difficult to establish at what structure they are looking or where a calcification is localized. The larger image amplifiers or television-type cinefluorographs should eliminate this confusion. The major drawback of the larger cinefluorographs is their initial cost. Also to use the full capability of the larger image amplifier, 35-mm. film is necessary, which in itself is more expensive. Some may object to the additional bulk of even the smaller image-amplifier tube. The benefits of the added information, however, far outweigh these minor disadvantages.

Summary

The additional important information obtained through cinefluorography warrants the use of this method in acquired heart disease. It is superior to all other methods for recording cardiac pulsations and calcifications. Its unique advantage for recording fat lines about the heart is extremely important. As the equipment improves, biplaned cinecardioangiography will be part of the armamentarium of all cardiac laboratories.

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*An almost complete bibliography on cinefluorography can be obtained by request from Eastman Kodak, Rochester, New York.

A particularly striking instance of Sydenham's penetrating observation and of his gift of graphic description is his account of St. Vitus' dance, now known universally as Sydenham's chorea: "St. Vitus's dance is a sort of convulsion which attacks boys and girls from the tenth year until they have done growing. At first it shows itself by a halting, or rather an unsteady movement of one of the legs, which the patient *drags*. Then it is seen in the hand of the same side. The patient cannot keep it a moment in its place, whether he lay it upon his breast or any other part of his body. Do what he may, it will be jerked elsewhere convulsively. If any vessel filled with drink be put into his hand, before it reaches his mouth he will exhibit a thousand gesticulations like a montebank."—DAVID RIESMAN, M.D. *Thomas Sydenham, Clinician*. New York, Paul B. Hoeber, Inc., 1926, p. 31.

ABSTRACTS

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ATHEROSCLEROSIS

Alekseeva, A. S.: A Study of Elastase Inhibitor in Patients with Atherosclerosis and Hypertensive Disease. Cor et Vasa **2**: 215, 1960.

Levels of elastase inhibitor in the serum of patients with essential hypertension and of those with arteriosclerosis showed no significant difference from those in normal blood donors.

LEPESCHKIN

George, E. P., Hall, G. V., and Farkas, G. S.: Lipaemic Clearing Action of Artificial Anticoagulants. Nature **187**: 782 (Aug. 27), 1960.

The authors investigated the in vivo clearing action of several anticoagulants using isotopically labeled fats. Heparin administered in a dose of 7,500 units every 4 hours trebled the rate of removal of alimentary lipemia; the artificial anticoagulants, phenindione, diphenadione, and 3(1-phenylpropyl)-4-hydroxycoumarin, were given to maintain the prothrombin time between 40 and 60 per cent with approximate doubling of the rate of removal of alimentary lipemia.

KALMANSOHN

Hollander, W., Chobanian, A. V., and Wilkins, R. W.: The Effects of Triparanol (MER-29) in Subjects with and without Coronary Artery Disease. J. A. M. A. **174**: 5 (Sept. 3), 1960.

Eighty-nine patients who had had serial cholesterol determinations for more than 2 years before the institution of the study were treated with triparanol. The age range was 24 to 76 years. Fifty-one were women and 38 were men. Of these, 43 had either clinical or electrocardiographic evidence of coronary artery disease, with angina pectoris in 28. In a maximally effective dose of 250 mg. triparanol per day, 71 of 89 subjects had significant reduction of serum cholesterol, whether or not they had previously had hypercholesteremia. The decrease in serum cholesterol (Abell) averaged 45 mg. per cent and ranged from 20 to 11 mg. per cent. The serum cholesterol to serum phospholipid ratio was also favorably influenced. Radioisotopic tracer substances indicate that this therapy not only reduces serum cholesterol but also the "miscible pool" of cholesterol in man. There is also reduction in total sterol content of the blood as well as the "total sterol pool." There was an antianginal effect in 12 of 28 subjects, and electrocardiographic improvement was noted in stress tests in three of 11 subjects with angina pectoris, associated with the fall in the serum cholesterol.

KITCHELL

McCullagh, E. P., and Lewish, L. A.: A Study of Diet, Blood Lipids and Vascular Disease in Trappist Monks. New England J. Med. **263**: 569 (Sept. 22), 1960.

A group of Trappist monks whose daily regimen included a diet low in animal fat, a peaceful life, and physical exercise were compared with

a group of healthy men of comparable ages. It was found that although the concentration of blood cholesterol in the monks was, on the average, considerably lower than that of the non-monks, the monks did not show a decreased incidence of arteriosclerosis and, in fact, had a higher incidence of hypertension. Thus, it would appear that diets low in animal fat and associated with relatively low serum cholesterol levels are not sufficient in themselves to prevent cardiovascular degeneration and arterial hypertension.

SAGALL

Segall, S., and Neufeld, A. H.: Blood Lipid Variations in Patients with Hypercholesterolemia and Coronary Artery Disease. Part I. Canad. M. A. J. **83**: 521 (Sept. 3), 1960.

All of 10 patients with hypercholesteremia and coronary artery disease showed considerable spontaneous fluctuation in blood lipids. During periods of 2 weeks or less the average cholesterol fluctuation from the mean was 28 per cent and the C/P ratio 19 per cent, whereas over a year's time the cholesterol varied 44 per cent and the C/P ratio 38 per cent. The changes could not be correlated with alterations in diet or weight. The stress of being ill and hospitalized was followed by a lowering of the cholesterol values in all of three instances. In contrast, blood lipids varied little in nine healthly middle-aged men studied over periods up to 1 month. Caution was advised in relating changes in blood lipids to various physiologic events.

ROGERS

BLOOD COAGULATION AND THROMBOEMBOLISM

Deaton, H. L., and Anlyan, W. G.: A Study of Experimental Methods for Producing Thrombosis in Small Arteries. Surg., Gynec. & Obst. **111**: 131 (Aug.), 1960.

Three methods for producing thrombosis in a temporarily isolated segment of the carotid or femoral artery of dogs were devised. First, injection into the segment of 100 units of thrombin solution caused a completely occluded thrombus that persisted for at least 3 weeks in 45 per cent of animals. Second, destruction of the segment's intima by injecting 0.1 normal sulfuric acid actuated thrombosis lasting up to 2 weeks in 75 per cent of trials. Third, surgical intimectomy was followed by occlusive clotting, persisting for as long as 6 weeks in 38 per cent of animals whose arteries were more than 3 mm. in diameter and for periods up to 3 weeks in dogs whose arteries were 2 to 3 mm. in diameter. The latter method was recommended for the experimental study of small artery thrombosis, a major problem in arterial surgery.

ROGERS

Griffith, G. C., Zinn, W. J., Engelberg, H., Dooley, J. V., and Anderson, R.: Heparin vs Heparin-Bishydroxycoumarin Therapy. J. A. M. A. **174**: 1157 (Oct. 29), 1960.

One hundred and sixty-three patients who entered the hospital and were classed as "severe cases of acute coronary occlusion" were used in this study. These patients had an acute myocardial infarction, plus one or more of the following conditions: shock, serious arrhythmia, second- or third-degree heart block, prolonged angina, heart failure or acute pulmonary edema, hypertension, diabetes, or a previous infarction. Throughout the acute illness, 100 received heparin (100 mg. subcutaneously every 12 hours). The bishydroxycoumarin group (63 patients) were given intravenous heparin along with the bishydroxycoumarin on admission; this was continued usually for 2 to 4 days until the bishydroxycoumarin had lowered the prothrombin time to 20 per cent of normal or below (Ware-Stragell technic). There were 12 thrombotic complications in the group treated with bishydroxycoumarin compared to five such incidents in the heparin group. There were five embolic complications in the heparin group compared to one in the bishydroxycoumarin group. Of 52 patients receiving adequate bishydroxycoumarin therapy, 16 died; of 12 considered to have inadequate therapy, eight died. Of 75 cases with adequate heparinization, 16 died; 12 out of 25 died with inadequate heparin therapy. Three or more complications were followed by death in 11 of 19 given bishydroxycoumarin and 14 of 60 given heparin. It was noted that peripheral arterial embolic complications were a greater hazard with heparin than with bishydroxycoumarin therapy when the drug was abruptly stopped and not resumed as soon as clotting times approached normal levels. In both groups a significant increase in morbidity was noted with inadequate treatment. In an overcrowded and understaffed hospital, heparin therapy permits more adequate anticoagulant therapy in severe myocardial infarction than bishydroxycoumarin.

KITCHELL

Laki, K., Gladner, J. A., and Folk, J. E.: Some Aspects of the Fibrinogen-Fibrin Transition. Nature **187**: 758 (Aug. 27), 1960.

The authors report on the enzymatic and polymerization phases of the fibrinogen transition to fibrin. Thrombin appeared to be a protease that

hydrolyzed arginylglycine bonds to liberate peptides. The hydrolytic action of thrombin is limited to a few peptide bonds in fibrinogen. The authors speculated that the peptides released may be important in local vasoconstriction. By electron microscopic examinations, the fibrinogen molecule appears to resemble a string of three beads with peptide A on the end and peptide B on the side. A factor appears to be manufactured in the bone marrow that prevents the normal plasma clot from being soluble in 8 M of urea. In certain diseases of metabolism involving the bone marrow this factor is missing.

KALMANSOHN

Soardi, F. G., Stefanini, M., Stump, D. J., and Marin, H. M.: The Components of the Fibrinolytic System in a Venous Segment Undergoing Experimental Thrombosis. Surg., Gynec. & Obst. **111**: 135 (Aug.), 1960.

Thrombosis was induced in a partially ligated jugular venous segment in eight dogs by injecting homologous serum intravenously. Plasma fibrinolysin activity increased slightly in the initial phase of clotting but returned to normal within 1 hour, both in blood from the general circulation and from the vein above the thrombosis. Blood from the vein below the thrombosis showed a fibrinolysin elevation for 1 to 24 hours. Profibrinolysin varied in a reciprocal manner. The slight elevation of fibrinolysin appeared ineffectual in controlling the propagation of the thrombus, which continued for several days. No significant change in proactivator, activator, or antifibrinolysin activity was found.

ROGERS

Wilson, J. S.: Fibrinolysin Treatment of Induced Venous Thrombosis in the Dog. Surgery **48**: 469 (Sept.), 1960.

The fibrinolytic activity of two commercial preparations of fibrinolysin was estimated in dogs in which a venous occlusion of a segment of small bowel was induced. Prothrombin times, venous clotting times, fibrinogen determinations, and lytic activity were determined. The latter was estimated by the lysis time of spontaneously clotted blood, oxalated plasma clotted with thrombin, serum with added fibrinogen clotted with thrombin, and fibrinolytic activity of the euglobulin fraction. The estimations of euglobulin fraction of fibrinolytic activity gave the most consistent results. Thrombosis was induced in a small series of dogs with no tendency toward dissolution of the clot or resolution of the compromised bowel circulation within 24 hours. A second small group of control animals was given fibrinolysin in varying doses. No thromboses formed and no deaths occurred The speed of lysis of the clot and return of color to the bowel were dependent upon the dose of fibrinolysin. Treatment was usually begun 60 to 90 minutes after thrombosis had taken place; the longest time being 5 hours. With large doses of fibrinolysin, the bowel usually began to resume its normal color before the infusion was finished and the thrombus was lysed 2 to 3 hours after the end of the infusion. Twenty-four hours later, the dogs were sacrificed and the vessels sectioned for gross and microscopic examination. The latter examination occasionally showed small fragments of clots still adherent to the intimal lining of vessels, which appeared to be free of clot grossly. This is probably related to the trauma to the vein during induction of the thrombus. Rethrombosis occurred in three dogs. In subsequent experiments this was prevented by the administration of heparin at the end of the fibrinolysin infusion. Fibrinolytic activity was usually maximal at the end of the infusion and then progressively diminished so that enhanced lytic activity was no longer present 3 to 4 hours after the infusion. Lytic activity did not seem related to in vivo fibrinogen concentration. There was good lytic activity present in some cases with little depression of fibrinogen. Conversely with large doses, lytic activity disappeared several hours before reappearance of measurable fibrinogen in the plasma. The fall in fibrinogen was most closely related to the number of units of fibrinolysin per kilogram of body weight administered per hour. The lowest fibrinogen levels usually occurred 2 to 4 hours after the beginning of the infusion and the fibrinogen then tended to return toward normal about 6 hours later and then temporarily rose to above the pre-infusion level. The prothrombin time was better correlated with the fall of fibrinogen than was the venous clotting time. In half the animals receiving fibrinolysin following induced thrombosis, the blood became incoagulable. When there was a break in the vascular continuity in such animals, such as a needle puncture, persistent hemorrhage occurred.

SHEPS

CONGENITAL ANOMALIES

Bedford, D. E.: The Anatomical Types of Atrial Septal Defect. Am. J. Cardiol. **6**: 568 (Sept.), 1960.

Of 185 consecutive patients subjected to open-heart surgery for correction of atrial septal defect, 170 were seen to have an ostium secudum (fossa ovalis) type. The opening was located in the center of the septum in 6 per cent, immediately above the inferior vena caval orifice in 26

per cent, and immediately below the superior caval orifice in 5 per cent. The latter (sinus venosus defect) was associated with anomalous drainage of the right pulmonary veins, the upper usually entering the superior cava, the middle entering the right atrium, and the lower draining into the left atrium. One patient had a nearly total absence of the atrial septum and another had a double defect with cor triatriatum. Fifteen patients had an ostium primum defect of whom two had normal A-V valves, 10 had a cleft mitral valve (three also had a tricuspid cleft), and three had a common A-V canal. The incidence of A-V cushion defects was believed to be much higher than this in infants and young children, few of whom have survived to undergo surgery. The diagnosis of the two major types of atrial defects was summarized and was usually possible by clinical means, sometimes aided by cardiac catheterization. Delineation of the structural abnormalities was believed important because correction of the simpler ones was carried out under hypothermia, whereas the more complicated ones required cardiopulmonary bypass.

ROGERS

Bender, F., and Doerr, F. F.: On the Diagnosis of Atypical Aortico-Pulmonary Communications. Ztschr. Kreislaufforsch. **49**: 695 (Aug.), 1960.

The first of four patients had normal pulmonary artery pressure, and showed a typical late systolic murmur continuing into diastole. The second patient had a higher pressure in the aorta than in the pulmonary artery only in systole while in diastole the two pressures were nearly equal; accordingly, only a systolic murmur was registered. The third patient showed almost identical pressure in pulmonary artery and aorta, and no murmurs were registered. In such cases cardiac catheterization is necessary for the diagnosis. In the fourth patient systolic pulmonary artery pressure exceeded that in the aorta, and a systolic murmur with marked accentuation of the second pulmonic sound was registered; the murmur was transmitted into the carotid artery. In this case diagnosis could be made even without catheterization as injection of dye into the cubital vein caused a bifid light absorption curve with early first summit from the left ear but a single curve with a late summit from the right ear.

LEPESCHKIN

Bouchard, F., and Wolff, F.: Hemodynamic Study of 150 Interventricular Septal Defects. Arch. mal coeur **53**: 617 (June), 1960.

Of 150 patients with ventricular septal defects submitted to cardiac catheterization, 15 showed normal right ventricular and pulmonary artery pressures, while 70 showed elevated pressures (30 to 95, on the average 65 mm. mercury); the shunt in the latter was always left-to-right as the systemic pressure exceeded right ventricular pressure. A third group of 45 patients showed elevated right ventricular pressures (34 to 120 mm.) with a marked drop of pressure between the inflow and outflow tracts (average 22 mm.) and a left-to-right shunt. The diastolic portion of the curve was ascending in the inflow tract and descending in the infundibulum; the systolic portion in the infundibulum was identical with that in the inflow tract except that its summit was cut off or even concave, as in infundibular stenosis. In a further group of 13 patients there was a pressure drop between the inflow tract and the pulmonary artery, but its localization could not be ascertained. In two patients there was a drop of pressure at the pulmonary valve; and in seven, a drop was found both at the infundibulum and the pulmonary valve. The age of the patients and the degree of the shunt did not differ appreciably in the four groups. In the first group there was apparently good adaptation of the pulmonary circulation to the increased blood flow, but in the second group this adaptation was deficient, resulting in pulmonary hypertension. The third and fourth groups were apparently characterized by a muscular spur in the infundibular region that caused a functional infundibular stenosis in systole. This spur was probably a congenital anomaly, since age did not play a role in its frequency, but in some cases the drop in pressure increased with age and was probably caused by muscular hypertrophy. The septal defect was usually located underneath the spur, and during open-heart surgery it was advisable to resect the spur while repairing the septal defect, if the pressure drop exceeded 20 mm. Hg. The infundibular pressure drop was sometimes masked by the appearance of extrasystoles while the tip of the catheter was passing this region; this could be avoided by using a double-lumen catheter and registering infundibular pressures from the lateral opening. The over-all effect of the spur and the resulting infundibular stenosis was to protect the pulmonary circulation from excessive pressures. In some instances increase of the stenosis could cause reversal of the shunt and appearance of cyanosis.

LEPESCHKIN

Burchell, H. B., DuShane, J. W., and Brandenburg, R. O.: The Electrocardiogram of Patients with Atrioventricular Cushion Defects (Defects of the Atrioventricular Canal). Am. J. Cardiol. **6**: 575 (Sept.), 1960.

Theoretical and practical considerations of the effects of an A-V cushion defect on the electrocardiogram were presented, and experience with 85 such cases was described. The cardinal and nearly diagnostic feature was an initial QRS vector directed in the 0 to (-) 60° sextant. This finding was attributed primarily to a congenital aberration of the left bundle-branch system, and the effects of mitral regurgitation were believed to be of lesser importance. The P-R interval was prolonged in 60 per cent, Q_{v6} was seen in 70 per cent, an rSR pattern indicative of volume overloading of the right ventricle was usually observed, and occasionally P mitrale or pulmonale was present. A number of other electrocardiographic changes were superimposed because of the presence of associated hemodynamic disturbances. The electrocardiogram was believed to be the most important single clinical indicator of the presence of an A-V cushion defect.

ROGERS

Craige, E.: Phonocardiography in Interventricular Septal Defects. Am. Heart J. **60: 51** (July), 1960.

Thirty-five patients with interventricular septal defects demonstrated at cardiac catheterization were studied phonocardiographically. When these patients were divided into three groups on the basis of pressures and flows in the pulmonary artery, it was found that each group had characteristic auscultatory findings. The group with low systolic pressure in the pulmonary artery and relatively small left-to-right shunts showed a loud, pansystolic, crescendo-decrescendo or constant-intensity murmur loudest in the third and fourth left intercostal spaces; no diastolic phenomena; a second sound that was normally to widely split, usually variable with respiration, and not accentuated; and no ejection sound. The group with moderate to severe pulmonary hypertension and large left-to-right shunts had a similar murmur; showed in diastole a third heart sound or a mid-diastolic murmur; had a second sound that when widely split was not variable with respiration; and sometimes revealed an ejection sound. The patients with severe pulmonary hypertension and smaller or mixed shunts showed a systolic murmur that was short, soft, early in systole and maximal in the second, third or fourth left intercostal space; demonstrated on occasion, pulmonary diastolic murmurs; had second sounds that were accentuated, narrowly split, or single; and showed ejection sounds in early systole. It is concluded that phonocardiographic study adds significantly to the evaluation of the physiologic disturbances in patients with interventricular septal defect.

SAGALL

Espino-Vela, J., Murad-Netto, S., and Rubio-Alvarez, V.: Differential Diagnosis between Persistent Atrioventricular Canal and the Combination of Atrial and Ventricular Septal Defects. Am. J. Cardiol. **6:** 589 (Sept.), 1960.

The clinical distinction between persistent A-V canal and the combination of atrial and ventricular septal defects was described, based on an experience with five and nine patients respectively. The physical, electrocardiographic, and plain roentgenographic findings were similar in the two conditions, but usually permitted distinguishing them from isolated atrial or ventricular septal defect. Withdrawal of a catheter from the left ventricle through the right ventricle, then into the right atrium suggested the presence of a persistent A-V canal. The detection of a ventricular shunt by a second catheter after the atrial defect had been occluded by a Dotter-Lukas catheter confirmed the diagnosis in one patient. The finding of mitral regurgitation at angiocardiography would favor the diagnosis of persistent A-V canal.

ROGERS

Heintzen, H., and Griese, M.: Unilateral Agenesis of the Pulmonary Artery. Arch. Krieslafforsch. **32:** 263 (June), 1960.

A case of unilateral agenesis of the pulmonary artery is reported and the literature on 71 published and documented cases of agenesis of the right or left pulmonary artery is surveyed. Whereas right-sided agenesis was often isolated or accompanied by benign cardiac or vascular anomalies, the absence of left-sided agenesis was often combined with tetralogy of Fallot or right-sided aortic arch. Clinically, the condition was characterized by slight asymmetry of the chest, exertional dyspnea, recurrent pulmonary infections, and occasionally hemoptysis. The affected side showed decreased pulmonary vascular markings, smaller hilus, decreased intercostal spaces, and a raised position of the diaphragm. The mediastinum was displaced toward the affected side. However, all these clinical and roentgenologic signs may be absent. The electrocardiogram usually showed no abnormality. The most certain method of demonstrating this lesion was by angiocardiography, although even this method may fail, particularly in the presence of accessory lung vessels. Cardiac catheterization was usually not required in uncomplicated cases. Bronchography may show bronchiectasis as well as associated hypoplasia or agenesis of the lung. Differential diagnosis includes agenesis or hypoplasia of the lung, atelectasis, and tumors with vascular compression.

BRACHFELD

McCormack, R. J. M., Marquis, R. M., Julian, D. G., and Griffiths, H. W. C.: Partial Anomalous Pulmonary Venous Drainage and Its Surgical Correction. Scot. M. J. 5: 367 (Sept.), 1960.

The embryologic, anatomic, physiologic, clinical, and surgical aspects of this subject are reviewed in detail and nine patients are reported. The anomalies were corrected surgically under hypothermia and there was one postoperative death attributed to multiple cerebral infarcts questionably due to air embolism. The clinical features resembled those of an ostium secudum type of atrial septal defect but the presence of sinus arrhythmia and electrocardiographic evidence of right ventricular hypertrophy rather than incomplete right bundle-branch block suggested the presence of anomalous pulmonary drainage. When the anomalous veins join the superior vena cava or the inferior vena cava, a plain film of the chest is usually characteristic. When the anomalous veins join the right atrium, neither cardiac catheterization nor dye-dilution technics can be relied upon to distinguish between anomalous veins and an uncomplicated atrial septal defect. Therefore, when undertaking surgical repair of atrial septal defects, the surgeon must be prepared to correct previously unsuspected anomalous pulmonary drainage. The prognosis and risk of operation are similar to those of uncomplicated atrial septal defect. The results of surgical treatment are satisfactory and the proper time for operation is as soon as there is clinical, electrocardiographic, and radiologic evidence of significant right ventricular overload.

SHEPS

Michaels, L., and Parkin, T. W.: Mild Congenital Heart Defects. J. A. M. A. 174: 491 (Oct. 1), 1960.

More reliable criteria for diagnosis of congenital heart disease were sought in a study of 128 subjects who submitted to cardiac catheterization. Forty-five of these were suspected clinically of having congenital heart disease but had normal findings on cardiac catheterization. Sixty-nine patients were proved to have mild congenital heart disease. Fourteen volunteer physicians with no clinical evidence of cardiac or pulmonary disease were also studied. Clinical evaluation of these patients showed a continuous murmur in all patients with persistent ductus arteriosus. In all but one patient with ventricular septal defect and in all patients with pulmonary valve stenosis (where the systolic gradient across the pulmonary valve was more than 31 mm.), a grade III or IV murmur was heard. This was widely transmitted or associated with a thrill in all cases. In all patients with an atrial septal defect and a left-to-right shunt of more than 25 per cent, either cardiomegaly or electrocardiographic abnormalities were present. On the basis of these criteria, it is possible to make a reasonably confident clinical diagnosis in adult patients with the lesions mentioned. In a minority of patients with more trivial defects, diagnosis might not be possible without resorting to cardiac catheterization; but, except under special circumstances, this would not seem to be of practical importance at the present time.

KITCHELL

CONGESTIVE HEART FAILURE

Dauphin, G.: A New Digitalis Drug: Acetyl Digitoxin. Clinical Study of 100 Patients. Arch. mal. coeur 53: 654 (June), 1960.

In 53 cardiac patients in failure three tablets of acetyl digitoxin were usually given every day for 6 days, then 3 days a week for a month, then two tablets 3 times a week, but the dose was varied according to individual need. Edema showed improvement in 30 of 32, oliguria in 40 of 43, dyspnea in all of 24, cardiomegaly in 24 of 30, and tachycardia in all patients. Polymorphous ventricular extrasystoles disappeared in all of eight patients, but atrial fibrillation was regularized in only two of 19. A left ventricular hypertrophy pattern showed improvement in five of 23 patients. In 46 patients with atrial fibrillation the drug was usually given in a dose of three tablets every day for 8 days. Of the 333 patients where fibrillation persisted, 10 could be later regularized with quinidine. One patient who had previously not responded to quinidine, did so to acetyl digitoxin. Of three patients with atrial flutter, two were converted to sinus rhythm after 15 to 28 tablets. Acetyl digitoxin should, therefore, always be tried in fibrillation and flutter before starting quinidine treatment. Three patients suffered arterial embolism during treatment and one developed complete atrioventricular dissociation after 10 tablets. Digestive disturbances appeared in 10, extrasystoles in four, paroxysmal tachycardia in one, atrial fibrillation in two, bundle-branch block in four patients, while 1 patient each developed urticaria, vertigo, and delirium. All these side effects disappeared after cessation of treatment. Typical S-T segment changes appeared in 56 of the 100 patients.

LEPESCHKIN

Davis, J. O., Carroll, W. R., Trapasso, M., and Yankopoulos, N. A.: Chemical Characterization of Cardiac Myosin from Normal Dogs and from Dogs with Chronic Congestive Heart Failure. J. Clin. Invest. 39: 1463 (Sept.), 1960.

The molecular size and chemical nature of cardiac myosin were determined in normal dogs and in dogs with chronic congestive heart failure. The molecular weight of normal cardiac myosin was found to be 500,000. No difference was observed between cardiac myosin from normal dog hearts and from either the right or left ventricle of dogs with right-sided congestive heart failure due to tricuspid insufficiency and pulmonic stenosis. The authors conclude that this study offers no support to the view that altered contractile proteins constitute the biochemical defect in the failing heart.

KARPMAN

Dodge, H. T., Lord, J. D., and Sandler, H.: Cardiovascular Effects of Isoproterenol in Normal Subjects and Subjects with Congestive Heart Failure. Am. Heart J. **60:** 94 (July), 1960.

Isoproterenol was administered intravenously to three subjects with normal cardiac function and to 18 subjects with congestive heart failure. During infusion of the drug it was found that the cardiac output and ventricular work were invariably increased; that the stroke volume and ventricular stroke volume were usually increased; that the peripheral venous pressure, peripheral vascular resistance, and arteriovenous oxygen difference were decreased; that the mean pulmonary arterial and systemic arterial pressures remained unchanged or showed only slight increase or decrease; and that oxygen consumption and heart rate rose moderately. It was concluded that this drug increased the strength of myocardial contraction in both normal subjects and those with congestive heart failure.

SAGALL

Glatt, B. S., and Rowe, R. D.: Cerebral Arteriovenous Fistula Associated with Congestive Heart Failure in the Newborn. Report of Two Cases. Pediatrics **26:** 596 (Oct.), 1960.

Two patients are reported in whom congestive failure in the newborn period was associated with a cerebral arteriovenous fistula. The first patient died at 5 months of age with advanced neurologic disease, the other died at 3 days in severe congestive heart failure. The arteriovenous fistulas induce cardiac enlargement and lower diastolic pressure secondary to increased cardiac output resulting from the short circuiting of blood and reduced peripheral resistance. Data on newborn infants have indicated that there is approximately a three-fold increase in the output of each ventricle after birth. Thus, any condition that would embarrass cardiac output shortly after birth could readily result in cardiac failure. A bruit may be heard over the skull in the presence of a cerebral arteriovenous fistula if the lesion is not deep seated as in the two patients presented. Neurologic changes, if they develop, often occur too late to be of help in early diagnosis.

SHEPS

Kunos, I., and Szabo, Z.: Seven Years of Experience with Ligation of the Iliac Veins for Treatment of Heart Failure. Ztschr. Kreislaufforsch. **49:** 11 (Sept.), 1960.

Ligation of the iliac veins is a less severe and dangerous procedure for decreasing venous return to the heart in cases of intractable heart failure than ligation of the inferior vena cava. Of 65 patients submitted to this operation and followed 1 to 6 years, nine showed marked improvement of dyspnea, hepatic enlargement, ascites and edema, 19 showed a satisfactory improvement, 13 remained unchanged, seven became worse, and two died as a result of the operation; six died later after a temporary improvement. In five patients with mitral stenosis the operation improved the circulation sufficiently to allow mitral commissurotomy after medical treatment failed to achieve this result. In two patients where commissurotomy was unsuccessful because of marked valvular calcification, iliac ligation brought marked improvement. Cyanosis of the legs usually disappears completely a few hours after operation; however, in two patients where ligation was carried out proximal to the inferior epigastric veins the ligature had to be removed because of increasing cyanosis.

LEPESCHKIN

NEWS FROM
THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, New York
Telephone Gramercy 7-9170

Applications for AHA Grants Are Due by November 1

November 1, 1961 is the deadline for submitting applications to the American Heart Association for grants-in-aid for the fiscal year beginning July 1, 1962.

Grants are made to non-profit institutions in direct support of a particular investigator for a specific program of research under his direction. Awards are in support of research in the cardiovascular field or basic sciences for periods up to five years.

Application forms are obtainable from the Associate Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, New York.

AHA Scientific Sessions Program

Abstracts of 165 original scientific papers, to be presented at the 34th annual Scientific Sessions of the American Heart Association from October 20-22 in Bal Harbour, Miami Beach, Florida, are included in Part II of this issue of *Circulation* (October). They were selected by the AHA Committee on Scientific Sessions Program from a record number of 627 abstracts submitted for consideration.

Papers will be presented during six sessions on clinical cardiology and at 15 other scientific sessions to be held simultaneously during the three-day program. Additional presentations will be made at panels, symposia and lectures.

The scientific program will open with a brief address by Oglesby Paul, M.D., AHA President, on Friday morning, October 20. This will be followed by the Conner Memorial Lecture, "Pathogenesis of Focal Cerebral Ischemia," by Clark H. Millikan, M.D., Professor of Neurology, Mayo Clinic. Saturday's program includes the Brown Memorial Lecture, "Physiology of the Peripheral Circulation," by Robert W. Wilkins, M.D., Professor of Medicine, Boston University School of Medicine, and presentation of the AHA Research Achievement Award.

Dr. Luther L. Terry, Surgeon General of the U.S. Public Health Service, will speak on "Heart Disease Control—A Joint Responsibility," at a luncheon sponsored by the Council on Community Service and Education on Saturday. The Association's Howard W. Blakeslee Awards for outstanding reporting in the cardiovascular field will also be presented at the Council's luncheon.

Conferences on a variety of cardiovascular subjects are scheduled for Saturday evening.

Sunday's program includes two sessions on cardiovascular films, with introductions and commentary by the author or other authority on the subject.

Those holding confirmed hotel reservations will receive advance copies of the program. Others may obtain programs at the registration desk or from their local Heart Association.

Heart Associations Donate $87,385 To Supplement AHA National Research

Contributions totaling $87,385 were received from Heart Associations through July 20, 1961, to supplement the national AHA research program for fiscal 1961-62.

In addition to those previously reported,

contributions over amounts regularly assigned by them for research have been received from Associations as follows:

Massachusetts Heart Association, $45,485, in full support of grants to Drs. Manfred L. Karnovsky, Harvard Medical School; Arnold S. Relman, Massachusetts Memorial Hospital, Boston; Stanford Wessler, Beth Israel Hospital, Boston; and Albert Szent-Gyorgyi, Institute for Muscle Research, Woods Hole, Mass. Also, Southeastern Chapter, Massachusetts Heart Association, $5,500 in full support of the grant to Dr. Robert Griesemer, Massachusetts General Hospital, Boston.

Mississippi Valley Heart Council of the Iowa Heart Association, $4,000 in partial support of the Research Fellowship of Dr. Elizabeth Vaughan-Potter, Northwestern University Medical School, Chicago.

Montana Heart Association, $5,000 in partial support of the grant to Dr. Verne L. van Breemen, Mercy Institute for Biomedical Research, Denver.

New York State Heart Assembly, Livingston County Chapter, $1,500 in partial support of the grant to Dr. William Lotspeich, University of Rochester; and Sullivan County Chapter, $1,000 to help support the grant of Dr. Alvan Feinstein at Irvington House, Irvington-on-Hudson.

These donations from Heart Associations make possible the support of studies approved by the AHA Research Committee which could not otherwise be financed by the national research budget.

New Film on Stroke Diagnosis Is Issued by Heart Association

A new professional film on strokes, which stresses the need for accurate differential diagnosis because of therapeutic advances in this field, has been produced by the American Heart Association and its affiliates.

Entitled "Cerebral Vascular Diseases: The Challenge of Diagnosis," the film presents three case histories involving cerebral thrombosis, hemorrhage and embolus, and depicts methods for proper diagnosis in each case.

The film's premiere showing will be at the Association's Annual Scientific Sessions in Bal Harbour, Fla., on Sunday, October 22, in the Americana Hotel. Subsequent showings for physician audiences will be arranged by affiliate and chapter Heart Associations throughout the country.

The film, in color, runs approximately 30 minutes. It is available for purchase or on loan from local Heart Associations or the American Heart Association, 44 East 23rd Street, New York 10, New York.

A companion piece to the AHA professional film "Cerebral Vascular Diseases: The Challenge of Management" produced in 1959, the new film was made by Churchill-Wexler Productions.

Meetings Calendar

October 17-19: International Seminar on Vascular Systems, Miami Beach. John B. Liebler, Heart Association of Greater Miami, 253 S.W. 8th St., Miami 36, Florida.

October 18-20: Council on Arteriosclerosis of the American Heart Association, Bal Harbour, Florida. Jeremiah Stamler, Chicago Board of Health, 54 W. Hubbard, Chicago 10, Illinois.

October 20-24: American Heart Association, Scientific Sessions, October 20-22; Annual Meeting, October 22-24, Bal Harbour, Florida. American Heart Association, 44 East 23rd St., New York 10, New York.

October 26-27: The Organization of Bio-Medical Instrumentation and Engineering in Universities and Hospitals, Omaha. Office of Medical Extension, University of Nebraska, Omaha 5, Nebraska.

November 13-17: American Public Health Association, Detroit. Berwyn F. Mattison, 1790 Broadway, New York 19, New York.

November 13-18: Canadian Heart Association and National Heart Foundation of Canada, Annual Meeting and Scientific Sessions, Vancouver. J. B. Armstrong, National Heart Foundation of Canada, 501 Yonge St., Toronto 5, Canada.

November 16-18: International Symposium "Etiology of Myocardial Infarction," Detroit. Thomas N. James, Henry Ford Hospital, Detroit 2, Michigan.

November 25-27: American College of Chest Physicians, Interim Session, Denver. Murray Kornfeld, 112 E. Chestnut, Chicago 11, Illinois.

November 27-29: American Society of Hematol-

ogy, Los Angeles. John W. Rebuck, Henry Ford Hospital, Detroit 2, Michigan.

November 27-30: American Medical Association, Clinical Meeting, Denver. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

December 1-2: Symposium on Cinefluorography (3rd), Rochester, New York. Stanley M. Rogoff, University of Rochester Medical Center, Rochester 20, New York.

December 8-9: New York Heart Association, Symposium on the Plasma Membrane, New York. Alfred P. Fishman, 10 Columbus Circle, New York 19, New York.

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January 29-February 1: American College of Surgeons, Sectional Meeting, Los Angeles. W. E. Adams, 40 E. Erie, Chicago 11, Illinois.

February 7-10: American College of Radiology, New York. W. C. Stronach, 20 No. Wacker Dr., Chicago 6, Illinois.

March 5-7: American College of Surgeons, Sectional Meeting, Detroit. W. E. Adams, 40 E. Erie, Chicago 11, Illinois.

March 26-28: American College of Surgeons, Sectional Meeting, Memphis. W. E. Adams, 40 E. Erie, Chicago 11, Illinois.

March 30-April 1: American Psychosomatic Society, Annual Meeting, Rochester, New York. Stewart Wolf, 265 Nassau Rd., Roosevelt, New York.

April 6-8: American Society of Internal Medicine, Philadelphia. G. T. Bates 350 Post St., San Francisco 8, California.

April 6-13: American Academy of General Practice, Las Vegas, Nevada. Mac F. Cahal, Volker at Brookside, Kansas City 12, Missouri.

April 9-13: American College of Physicians, Philadelphia. E. C. Rosenow, Jr., 4200 Pine St., Philadelphia 4, Pennsylvania.

April 16-18: American College of Surgeons, Sectional Meeting, Washington, D.C. W. E. Adams, 40 E. Erie, Chicago 11, Illinois.

April 29: American Federation for Clinical Research, Atlantic City. J. E. Bryan, 250 W. 57th St., New York 19, New York.

Abroad

1962

October 7-13: Fourth World Congress of Cardiology, Mexico City. I. Costero, Secretary General, Ave. Cuauhtemoc 300, Mexico 7, D.F.

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AMERICAN HEART ASSOCIATION

34TH SCIENTIFIC SESSIONS

BAL HARBOUR, MIAMI BEACH, FLORIDA

OCTOBER 20-22, 1961

Abstracts of Papers

(Listed alphabetically by first author)

(P) *Papers presented at the Scientific Sessions*

* *Established Investigator, American Heart Association, 1960-1961*

† *Research Fellow, American Heart Association, 1960-1961*

(A complete Program of all events is being printed separately.)

ABSTRACTS OF LECTURES

LEWIS A. CONNER MEMORIAL LECTURE

Pathogenesis of Focal Cerebral Ischemia

Clark H. Millikan, M.D.

The term "focal cerebral ischemia" embraces a spectrum of altered physiology, which extends from transitory attacks of focal cerebrovascular insufficiency, as defined by the clinician, at one end, to massive cerebral infarction, as defined by the neuropathologist, at the far extreme. In 1883, Brunton, partially as a result of stimulus from his teacher, DuBois-Reymond, discussed the possibility that cerebral arterial spasm might decrease blood flow to a local area of the brain, thus producing transient neurologic phenomena. The pathologist's unsuccessful attempts to detect obstruction in the intracranial artery supplying blood to an infarcted area, in many instances, has nurtured the "vasospasm theory" as the genesis of focal cerebral ischemia. Hunt's description of extracranial carotid occlusion was generally ignored until the last decade, when the frequent occurrence of this lesion was emphasized. Since 1955, several investigators have observed significant degrees of stenosis of the extracranial portion of one or more major cerebral arteries in many patients dying from a wide variety of causes. In certain of these patients, there was clinical evidence of focal cerebrovascular insufficiency, but the brain was normal. In others, there was clinical evidence of cerebral infarction, and a cerebral infarct was observed at necropsy. A third large group had neither clinical nor pathologic evidence of focal cerebral ischemia, but there was atherosclerosis so severe that one or more major cerebral vessels were occluded. It is apparent that some factor or factors must be added to the stable change in the lumen produced by atherosclerosis in order to cause significant focal cerebral ischemia. These additional factors, which include failure of the collateral circulation, "vasospasm," transient systemic hypotension, anemia, polycythemia, arterial kinking, external compression, thrombosis, and emboli from atherosclerotic lesions, will be analyzed and discussed with presentation of appropriate data.

GEORGE E. BROWN MEMORIAL LECTURE

Physiology of the Peripheral Circulation

Robert W. Wilkins, M.D.

During twenty-five years, my colleagues and I have sustained an interest in the physiology of the peripheral circulation, especially as it is affected by changes in environment, position, disease states, and procedures designed to improve it. Beginning with Soma Weiss, we examined the role of peripheral blood flow, venous tone, and venous pressure in syncope and collapse and in congestive failure, especially that of beri beri heart disease. This led to the finding that component parts of the circulation do not always act homogenously—constricting or dilating uniformly together—but rather may act independently, both as regards certain body areas and the volume-regulating venous, as distinct from the flow-regulating arteriolar, elements of the circuit.

During a year's sojourn in London with E. A. Carmichael, Joseph Doupe, Henry Newman and I learned with the digit plethysmograph about the extraordinary lability of the blood flow in the fingers and toes, where during full dilatation blood may rush (presumably mostly through shunts) in a volume of flow up to 100 times greater than that during vasoconstriction. Such increases in blood flow were found to cause digital arterial blood pressure to fall during full vasodilatation of the hand to 20 to 30 mm. Hg (systolic) lower than in the arm.

With Ludwig Eichna in Baltimore, studies were done on blood flow in the forearm and calf and on the marked vasodilating effects of metabolic activity produced either by reactive hyperemia, by exercise or by hyperthyroidism. Eichna also demonstrated the effects of local vasomotor activity on capillary blood pressure in the digits.

Returning to Boston in 1940, the peripheral and general vascular effects of angiotonin (Page) were studied with C. A. Duncan, and it is of current interest that those results have been recently corroborated, using synthetic angiotensin and modern methodology. With C. K. Friedland, John Hunt, and Meyer Halperin, investigations were made of the effects of changes in venous pressure, local limb compression, and limb position upon blood flow in the extremities. Later, with Edward Freis and

Joseph Stanton, it was shown that low levels of compression on the extremities may decrease the veins in diameter sufficiently to increase the velocity of flow in them, even though the volume of flow is slightly decreased. This finding was applied clinically through the use of elastic stockings to prevent phlebothrombosis.

During the war, there was a busy, stimulating association with Stanley E. Bradley, who brought the cardiac catheter to Boston, where he used it mainly to study hepatic blood flow. In the course of aviation medicine studies, we found some curious venous pressure and arterial pressure changes to occur under certain situations, such as the head-down position. The most remarkable of these was the finding that an elevation of *diastolic* pressure may occur in the brachial artery below a blood pressure cuff inflated on a relatively vasoconstricted arm at a pressure between the systemic systolic and diastolic arterial pressure.

With James Culbertson, studies were then done on sympathetic vasopressor responses to various stimuli, especially to the Valsalva maneuver. Such pressor overshoots were abolished by a Smithwick lumbodorsal splanchnicectomy. Later with Walter Judson, Donald Hatcher, and Paul Stucki, these Valsalva responses were shown to be markedly altered also in congestive heart failure.

Recently, with Julius Litter, J. Edwin Wood, Jack Eckstein, and Jay Coffman, we have returned to plethysmography, especially for re-examination of peripheral venous tone, venomotor and vasomotor responses. These studies show that venoconstriction occurs in congestive heart failure and in collapse, and that vasoconstriction does indeed occur after cigarette smoking.

Useful New Safety Measures for Closed Mitral Commissurotomy

Osler A. Abbott, Atlanta, Georgia

Many cardiovascular surgeons are concerned with technical dangers associated with teaching residents procedures in closed technic mitral commissurotomy. One major danger has been tears of the left atrium. In the last 50 cases, we have placed a long oval strip of compressed Ivalon about the base of the left atrium. Four traction sutures at the distal end of the appendage, placed about a cruciate incision, allow hemostasis. The Ivalon strip decreases clamp trauma to the atrium and decreases chance of atrial tear. Certain dangers of intra-atrial digital maneuvers have been emphasized (trauma to septal area, circumflex coronary artery, chordae, etc.).

Indications for and value of retrograde commissurotomy ("Logan maneuver") have been analyzed. The value of a square patch of pericardium or Teflon sewn to the epicardium at the site of the left ventricular incision lies in (1) prevention of left ventricular fracture, (2) decreased chance of purse-string suture cutting through during surgical maneuvers, and (3) decreased chance of postoperative left ventricular aneurysm.

Factors Influencing Successful Use of Left Subclavian Artery for Correction of Long Segments of Coarctation of the Aorta

Osler A. Abbott, Arthur T. Haebich, and E. R. Duschesne, Atlanta, Georgia

Although the majority of coarctations can be corrected by direct end-to-end anastomosis, a large segment of aorta may need to be resected if (*a*) a long area of coarctation presents or (*b*) significant aneurysmal disease of intercostal arteries is found. In children, it would be preferable to use viable tissue to repair the defect. One human case of 7 initially repaired by use of the left subclavian artery (1) had no relief from hypertension and (2) developed aneurysms at the site of origin of the left subclavian artery. Secondary resection with graft insertion was required.

A comparison of the value of 2 types of suture line at the site of transection of aorta just distal to the left subclavian artery was performed on dogs. Suture lines "parallel to" or "at right angles to" direction of aortic blood flow were tested. Analysis involved comparative studies of (1) direct pressure measurements at the level of aortic arch, left subclavian artery, and aorta distal to anastomosis; (2) angiographic studies immediately after anastomosis and in long-term survival animals; (3) digestion cast studies of such animals. Aneurysmal disease of the proximal portion of the left subclavian artery, similar to that in our human case, was reproduced in the dog when the suture line paralleled the aortic blood flow. Satisfactory results accompany the transverse type of suture line. This technic has been applied in subsequent human cases.

Observations on the Mechanism of the Local Vasodilator Effect of Guanethidine Seen in Man and in Dog

Francois M. Abboud† and John W. Eckstein, Iowa City, Iowa*

We have observed transient vasodilatation followed by sustained vasoconstriction in perfused denervated forelimbs of dogs after intra-arterial injections of guanethidine. The present experiments were done for 2 reasons: (1) to see if a similar biphasic response occurs in man and (2) to study the mechanism of the vasodilatation.

Graded doses of guanethidine were injected into the femoral arteries of 4 normotensive men. These doses did not alter systemic pressure or heart rate. Blood flow (plethysmograph) in the calf increased progressively with increasing doses of guanethidine. This transient vasodilatation was followed by sustained vasoconstriction as in the dogs.

Denervated forelimbs of anesthetized dogs were perfused at constant rates. Guanethidine and other vasodilator drugs were injected into the brachial artery before and after pretreatment with various blocking agents. Atropine antagonized the vasodilator response to methacholine in 8 dogs but had no effect on the dilator responses to guanethidine or glyceryl trinitrate. Antihistamines inhibited histamine vasodilatation in 7 dogs without affecting the guanethidine or glyceryl trinitrate responses. In 10 dogs, dichloroisoproterenol blocked the dilator effect of isoproterenol and inhibited the dilator response to guanethidine significantly without altering the glyceryl trinitrate response. There was no response to tyramine and only vasodilatation following guanethidine in 6 dogs pretreated with reserpine.

Transient local vasodilatation followed by vasoconstriction was seen in man after intra-arterial guanethidine. In dogs, the vasodilatation did not appear to be mediated by acetylcholine, histamine, or catecholamines. It may have resulted from stimulation of beta adrenergic receptors.

Functional Paroxysmal Ventricular Tachycardia

Crawford W. Adams, Nashville, Tennessee

Paroxysmal ventricular tachycardia is generally considered a manifestation of grave underlying organic heart disease. It should be recognized that in approximately 10 per cent of patients reported

with this arrhythmia, no underlying organic heart disease is found. The criteria for the diagnosis of functional paroxysmal ventricular tachycardia include (*a*) a succession of 4 or more independent ventricular contractions, (*b*) electrocardiographic evidence for ventricular origin, and (*c*) no demonstrable underlying cardiovascular disease.

A series of 9 patients was studied at Vanderbilt University Hospital during the past 18 years. Their ages ranged from 2 months to 40 years. All are presently living and in good health. Thirty other patients with the diagnosis of paroxysmal ventricular tachycardia were found to have either organic heart disease or the Wolff-Parkinson-White syndrome.

Valuable contributions by physiologists of the nineteenth century have not been sufficiently emphasized. In 1871, Roy and Adami demonstrated independent ventricular activity twice as fast as the atrial rhythm with the myocardiograph, and in subsequent years, Gibson, Wenckebach, McKensie, and Lewis were able to document clinical ventricular tachycardia. Recent electrophysiologic studies of cardiac muscle suggest mechanisms which may be responsible for the production of ventricular tachycardia.

Although occurring spontaneously, this arrhythmia is more commonly found with changes in the serum electrolytes. With short paroxysms, symptoms are unimpressive; however, significant hemodynamic clinical findings should suggest the diagnosis. Usually, this arrhythmia satisfactorily responds to simple measures of treatment, but with prolonged paroxysms, specific therapy with electrolytes, quinidine, or procaine amide is required.

Persistent Common Atrioventricular Canal Associated with Pulmonary Valvular or Infundibular Stenosis

Magnus H. Agustsson, Benjamin M. Gasul, and Rene A. Arcilla, Chicago, Illinois

Persistent common atrioventricular canal associated with pulmonary valvular or infundibular stenosis is rare. Only 7 cases have been reported in the literature, and none had angiocardiographic studies. During the last 10 years, we have observed 8 patients with this entity, 7 of whom came to autopsy. The ages ranged from 1 month to 8 years. Aside from the conventional phonocardiograms, chest roentgenograms, and electrocardiograms, venous and/or selective angiocardiograms were obtained in 6 patients and cardiac catheterizations in 3. The outstanding clinical and laboratory findings were as follows: Five patients had dyspnea, and 6 were clinically cyanotic. The second heart sound was single and loud. A pansystolic murmur was maximally located at the left lower sternal border in 3 patients and at the apex in another 3. Two patients had an additional stenotic murmur at the pulmonic area. Two patients in heart failure who died at 1 month of age had no murmurs. The chest roentgenograms showed mild to moderate cardiomegaly with elevated apex and concavity in the pulmonic area. The pulmonary vascular markings were normal or diminished. The electrocardiogram showed left axis ranging from –90 to –170 with counterclockwise rotation of the superiorly oriented vector forces in the frontal plane and marked right ventricular hypertrophy. Cardiac catheterization and angiocardiography demonstrated pulmonary stenosis and bidirectional shunting at the atrial and ventricular levels.

The clinical diagnosis can be strongly suspected on the basis of cyanosis, harsh pansystolic murmur located maximally at the left lower sternal border or apex, an additional stenotic murmur at the pulmonic area, chest roentgenograms compatible with tetralogy of Fallot, and electrocardiograms indicative of common atrioventricular canal. The diagnosis may be further established by catheterization and angiocardiography.

Spontaneous Closure of Ventricular Septal Defect in Eight Children Demonstrated by Serial Cardiac Catheterizations and by Angiocardiography

Magnus H. Agustsson, Benjamin M. Gasul, Rene A. Arcilla, Juan P. Bicoff, and Rogelio Moncada, Chicago, Illinois

Out of 480 children with ventricular septal defect seen by us during the last 15 years, the murmur disappeared in a considerable number of patients, but not all of those have had serial cardiac catheterizations or angiocardiography. Out of 195 patients who had cardiac catheterization, 55 had repeat cardiac catheterization and angiocardiography. Eight patients out of the latter group demonstrated spontaneous disappearance of the left-to-right shunt over periods varying from 11 months to 3 years. Initially, a grade 3 to 4 pansystolic murmur was present at the left lower sternal border in all 8 patients; a thrill and middiastolic rumble was present in 4 of them. On subsequent examinations, the murmur disappeared in 1 patient, and in 4 only an insignificant ejection murmur was present at the pulmonary area. In 3 patients, a grade 2 pansystolic murmur was still present, and a selective pulmonary artery and left ventricular angiocardiogram demonstrated a small left-to-right shunt in 2 of them. In 4 of these patients, chest roentgenograms and electrocardiograms revealed cardiomegaly, hypervascularity, and left ventricular hypertrophy on first examinations. On subsequent examinations, all

these findings became normal. The original cardiac catheterization revealed a left-to-right shunt varying from 1.10 to 8.10 L./min./M.^{2} in all 8 patients, but on repeat catheterization, the oxygen saturation data and even dye-dilution curves failed to demonstrate shunts in any of these patients. Our experience has not confirmed the previous reports that patients with spontaneous closure of ventricular septal defects usually present the so-called "puffy" or "disappearing-type" murmurs, since none of these 8 patients had this type of murmur. In 2 of our patients who presented a loud pansystolic murmur at the third to fourth left intercostal spaces, left ventriculography revealed that the defect was in the muscular septum.

Diagnosis of Bilateral Stenosis of the Primary Pulmonary Branches Based on a Characteristic Pulmonary Trunk Pressure Curve (P)

Magnus H. Agustsson, Sami Nassif, Rene A. Arcilla, Bessie L. Lendrum, and Benjamin M. Gasul, Chicago, Illinois

Hemodynamic and angiocardiographic studies were performed on 12 patients with bilateral stenosis of the primary pulmonary arteries. Right ventricular systolic pressures ranged from 33 to 145 mm. Hg. An abnormal pressure curve from the pulmonary trunk was consistently obtained. Pressure curves of the right ventricle and pulmonary trunk had identical contours and timing during systole. The pulmonary trunk showed wide pulse pressure due to elevated systolic but normal diastolic pressures. In mild stenosis, the dicrotic notch was located higher, was not deep, and had a gradually descending diastolic curve. In moderate stenosis, the diastolic notch was deep, and the curve showed a slower descent. In severe stenosis, the dicrotic notch was still deeper, almost equal to the early diastolic dip of the right ventricle, and was followed by a plateau-type curve. Angiocardiography demonstrated that stenotic areas widened during systole and narrowed during diastole. The pulmonary trunk functions as an outlet chamber during pulmonary ejection, and the valves remain open as long as right ventricular pressure is greater than that of the peripheral pulmonary vessels. In severe stenosis, elastic recoil of the pulmonary trunk during diastole does not produce significant forward displacement of blood. Consequently, pressure in this chamber is nearly constant throughout diastole and assumes a plateau-type curve. In milder stenosis, diastolic run-off still occurs, thus explaining the descending slope. The presence of these characteristic pressure curves in all 12 patients should permit the diagnosis of bilateral stenosis of the pulmonary arteries, even if these vessels cannot be entered.

Importance of Selective Angiocardiography in the Differential Diagnosis of Pulmonary Hypertension (P)

Umit T. Aker, Hakan Arvidsson, and Brent M. Parker, St. Louis, Missouri

The cause of pulmonary hypertension can often be determined from hemodynamic data obtained at right heart catheterization. Not infrequently, however, catheterization is incomplete for technical reasons or is inconclusive. Therefore, cases with increased pulmonary pressure may be incorrectly classified as primary pulmonary hypertension. Primary pulmonary hypertension is a diagnosis of exclusion only and, as such, cannot be made until all identifiable causes of increased pressure are eliminated. In our laboratory, supplementation of catheterization findings with selective angiocardiography has furnished definitive diagnostic information in 4 groups of patients with pulmonary hypertension: (1) Visualization of the left heart after contrast injection into the pulmonary artery permitted a diagnosis of aortic or mitral valve disease or left ventricular failure which was of special value when valid pulmonary capillary (wedge) pressures could not be obtained. (2) Selective angiography allowed demonstration of a ventricular septal defect or patent ductus arteriosus with balanced or right-to-left shunts. (3) Opacification of the pulmonary vasculature permitted differentiation of obliterative lesions which could otherwise have been classified as idiopathic pulmonary hypertension. These lesions include pulmonary embolization and multiple peripheral pulmonary artery stenoses. The latter is indistinguishable from primary pulmonary hypertension without angiocardiography. (4) The origin of right ventricular hypertension may remain unidentified after catheterization if the pulmonary artery cannot be entered. In this situation, angiography may establish the presence or absence of right ventricular outflow tract obstruction and delineate anatomic details not accessible with any other technic.

In our opinion, evaluation of patients with unexplained pulmonary hypertension is incomplete without selective angiocardiography.

Electron Microscopy of Cardiac Muscle During and After Cold Cardioplegia (P)

Harold M. Albert, Anthony Kattine, Bert A. Glass, and Ben O. Spurlock, New Orleans, Louisiana

Dogs were placed on cardiopulmonary bypass, and cold cardioplegia was obtained by several methods. The aorta was then cross-clamped so that the heart was completely anoxic, but the cardiac muscle temperature was maintained be-

tween 6 and 14 C. Biopsies were taken of the ventricular muscle prior to cardiopulmonary bypass, at intervals during the period of cardioplegia, and, finally, after the animal had resumed his own circulation and was normothermic.

Five minutes after arrest, electron microscopy showed the only change to be beginning loss of contraction nodes. At 20 minutes, there was almost complete loss of contraction nodes but essentially no change in the mitochondria or nuclei. At 40 minutes, there was occasional swelling of the mitochondria and clumping of the nucleoplasm. At 60 minutes, mitochondrial swelling and clumping of the nucleoplasm were slightly more frequent but still not common. There was no change in the myofibrils or striations. Thirty minutes after discontinuing cardiopulmonary bypass and restoring circulation, the specimens showed marked swelling and frequently complete dissolution of the mitochondria. Practically all nuclei showed clumping of the nucleoplasm, but the myofibrils continued to show little or no change. If circulation was restored after only 30 to 35 minutes of cold arrest with anoxia, the final biopsy after restoration of circulation showed little change.

Normothermic controls showed nuclear and mitochondrial changes beginning after only 20 minutes of anoxia and marked progression thereafter.

Distribution of Systemic Blood Flow in Extreme Obesity (P)

James K. Alexander, Houston, Texas, William G. Smith, Shenton Park, West Australia, Kamel H. Amad, Jerusalem, Jordan, W. Christopher Duncan, and Robert C. Austin, Houston, Texas

To investigate further the observation that circulating blood volume and resting cardiac output are increased considerably in extremely obese subjects, distribution of systemic blood flow has been assessed by means of the nitrous oxide method for cerebral flow determination (14 subjects), the bromsulfalein extraction method for splanchnic flow (11 subjects), and the p-aminohippuric acid clearance technic for renal flow (18 subjects). Cerebral flow and oxygen utilization were normal. Renal flow was normal or somewhat reduced. Splanchnic flow and oxygen utilization were increased but not sufficiently to account for the observed increment in cardiac output. Although no direct measurements of blood flow to fat tissue have been made, it may be inferred that the increase in cardiac output with obesity is distributed largely to fat tissue depots.

Mean blood volume and flow per unit weight of body tissue were 55 per cent and 60 per cent, respectively, of the predicted normal in 40 extremely obese subjects. Similarly, the increments in blood volume and flow per unit of excess weight were only 20 per cent and 30 per cent of the amounts found normally per Kg. body weight. It has been concluded from these observations that although blood volume and flow per unit weight of tissue are less in fat than in lean body mass, the accumulation of massive fat depots leads to high cardiac output and a markedly increased demand in terms of cardiac performance.

Endotoxin Shock—With Particular Reference to Lymph of Abdominal Organs

Fikri Alican and James D. Hardy, Jackson, Mississippi

The mechanism of endotoxin shock has been studied in 150 dogs by correlating the qualitative and quantitative changes in lymph of abdominal organs with other neurovascular parameters. A method was used to record lymph flow continuously (drops/time) which involved the use of a weight transducer and Sanborn recorder after catheterization of thoracic duct or the intestinal and liver lymph ducts.

Following I.V. endotoxin administration, there was a prompt increase of liver lymph which paralleled the rise of portal vein pressure (PVP), both coming back to normal in 15 to 30 minutes. Increase in intestinal lymph flow occurred gradually and covered the entire shock period. Also, the liver and intestinal components of the thoracic duct lymph flow curve could be recognized as such. In Eck-fistula dogs, this curve consisted of the intestinal component only, and PVP did not rise; these dogs did not live longer, however, and the usual hemorrhagic mucosal lesions and congestion of the intestines were not prevented. Thus, the initial hemodynamic changes taking place in the liver were not essential for the progression of shock. Lethal outcome appears to depend on changes in intestinal vasculature.

Erythrocyte and hemoglobin content of lymph increased; proteins decreased. Cardiac output and blood volume decreased, while myocardial force was only indirectly affected. Corticoids and catechol amines frequently rose to high levels. Dibenzyline pretreatment did not influence the hemodynamic alterations. Effect of total sympathectomy is being investigated.

Alteration in Myofibrillar Adenosine Triphosphatase in Human Congestive Heart Failure (P)

Norman R. Alpert and Michael S. Gordon, Chicago, Illinois

The experiments reported herein were designed to test the hypothesis that myofibrillar adenosine triphosphatase activity is low in the failing hu-

man heart. Myofibrillar ATPase from 7 failing and 9 control hearts was studied. The failing hearts came from patients with a clinical diagnosis of congestive heart failure following benign essential hypertension. This was always confirmed with a pathologic diagnosis of the disease, including evidence of hypertrophy, dilatation, and increase in heart weight. The normal hearts were obtained following traumatic death in otherwise normal subjects with no evidence of pathology and a heart weight less than 375 Gm. In the normal group, increasing $MgCl_2$ concentration increased the myofibrillar ATPase activity (μM Pi liberated per unit time per mg. protein) from 0.34 to 0.99 μM/mg./15 min., while in the failing group, the ATPase activity rose from 0.25 to 0.69 μM/mg./15 min. There was a significant correlation between myofibrillar ATPase activity and $MgCl_2$ concentration in both the failing ($P < .001$) and normal hearts ($P < .001$). The slopes of the 2 regression lines were different ($P < .02$). Thus, as the $MgCl_2$ concentration was increased, the ATPase from the failing hearts exhibited a significantly lower rise than that from the normal hearts. Increasing the substrate concentration to 5 mM ATP increased the myofibrillar ATPase activity to an optimum of 0.99 μM/mg./15 min. in the normal group and 0.69 μM/mg./15 min. in the failing group. Further increases in substrate concentration decreased the ATPase activity in both groups. At all substrate levels between 1 and 10 mM ATP, the myofibrillar ATPase activity was significantly lower in the failing group. Studies on the effect of time after death on myofibrillar ATPase activity indicate no change from 2 to 14 hours in human hearts and no change from 0 to 6 hours in dog hearts. Therefore, the heart myofibrillar ATPase activity from tissues taken up to 14 hours after death is a reflection on the antemortem activity. Thus, it is concluded that myofibrillar ATPase activity is decreased in human heart failure.

Helium-Oxygen Inhalation Test: A Simple Test for Identification of Small Left-to-Right Shunts

Kurt Amplatz, Yang Wang, and Paul Adams, Jr., Minneapolis, Minnesota

Because small left-to-right shunts are frequently missed during right-heart catheterization by measuring differences in blood oxygen content at various levels, numerous more sensitive technics have been devised. The helium-oxygen inhalation test is sensitive and has the advantage of simplicity. The technic entails depressing the systemic blood oxygen saturation by the inhalation of an inert gas and then rapidly raising it by breathing 100 per cent oxygen. Blood is simultaneously and continuously sampled from a selected site in the right heart at a constant rate through a cuvette oximeter. A left-to-right shunt upstream to the catheter tip will cause an earlier rise in oxygen saturation than in its absence. This procedure can be repeated at different sites for localization purposes.

In 13 patients so studied, helium was used as the inert gas because of its marked diffusibility. With no left-to-right shunt, the appearance time for a rise in venous oxygen saturation was delayed, and the time-saturation curve was flattened and prolonged. With a left-to-right shunt, the appearance time was foreshortened, and the curves showed steeper build-ups. Shunts were confirmed by oxygen saturation data, radioisotopic methods, and indicator-dilution curves. There were no false positives or negatives, complications, or discomfort during the brief hypoxemia. Two shunts not evident by oxygen saturation data were detected. It is felt that the helium-oxygen inhalation test warrants continued study as a safe, sensitive, and simple method for detecting and localizing small left-to-right shunts which can be carried out in any laboratory equipped to do oximetry.

Clinical and Hemodynamic Changes Following Mitral Annuloplasty (P)

Arthur M. Anderson, Leonard A. Cobb, Robert A. Bruce, and K. Alvin Merendino, Seattle, Washington

Eleven of 13 patients surviving open-heart mitral annuloplasty were evaluated 4 to 41 (average 19.4) months postoperatively. Exertional palpitation, fatigue, and dyspnea decreased in 10. Preoperative functional capacity was class IV in 3 and class III in 8; postoperatively, there were 1, 7, and 3 cases in classes III, II, and I, respectively. Intensity of the apical pansystolic murmur decreased in 9 and disappeared in 1. Size of left atrium and ventricle diminished in 10; left ventricular size became normal in 5. Precordial QRS voltage decreased in 9. Physical fitness index for treadmill walking increased to normal range in 6.

Mean resting cardiac index increased 0.5 L./min./M.^{2} in the 9 patients studied. Stroke index rose from 31 to 39 ml./M.^{2}, increasing in 7, decreasing slightly in 2. AV oxygen difference fell 12 ml./L. Mean pulmonary arterial pressure fell in 8, while it increased in another. Indicator-dilution curves showed less abnormal mixing in all. Mitral regurgitation was quantitated postoperatively in 6 with biplane angiocardiograms. Ratios of regurgitant to total stroke volume were 0, 0, 0.21, 0.24, 0.35, and 0.46. Two exhibited mitral stenosis postoperatively; in another, there

was recurrent regurgitation following initial improvement.

Best results were associated with absence of valvular calcification, pulmonary hypertension, or aortic regurgitation. Mitral annuloplasty in properly selected patients is an effective palliative procedure in patients with gross regurgitation evidenced by class III to IV functional capacity, marked left heart enlargement, and regurgitant flow equal to or exceeding forward flow.

Treatment of Acute and Chronic Edema by Extracorporeal Ultrafiltration (P)

Sidney Anthone and Roland Anthone, Buffalo, New York

The rapid removal of fluid from patients in acute pulmonary edema or protracted congestive heart failure is possible by ultrafiltration with an extracorporeal dialyzing unit. This is accomplished with the MacNeill dialyzer by reducing the atmospheric pressure around the blood cellophane tubes, thus establishing an increased hydrostatic gradient across the cellophane barrier. This results in the passage of plasma water and filtrable solutes across the membrane without depletion of proteins and cellular elements of the blood.

Varying amounts of subatmospheric pressure are produced around the cellophane tubes by attaching a suction apparatus to the bath line of the dialyzer. A hydrostatic gradient of 600 mm. Hg can thus be produced which will result in the extraction of about 1 L. of filtrate per hour. At higher pressure gradients, the high rate of filtration will gradually diminish or, in some cases, will result in hypovolemia, as evidenced by marked fall in blood pressure. This suggests that dehydration of the vascular compartment exceeds the rate of fluid shift from the interstitial space to the vascular space. It is because of this finding that we now restrict the rate of ultrafiltration in adults to not more than 1,000 cc. per hour.

The clinical response to this type of treatment has been very dramatic. Weight losses of up to 16¾ pounds have been recorded during a 6- to 8-hour procedure. Aside from the immediate improvement in cardiorespiratory function, many patients who were previously intractable will become sensitive to diuretics and reduce their remaining edema fluid.

True Truncus Arteriosus: Review of Seventeen Cases and Report of Surgery in Seven Patients

Robert M. Armer, Paulo F. DeOliveira, and Paul R. Lurie, Indianapolis, Indiana

In the past decade, 17 patients with true truncus arteriosus have been studied. Only cases with pulmonary arteries arising as 1 or 2 vessels from the ascending aorta were included. Ages ranged from 3 days to 9 years. Diagnosis in every case was finally confirmed by cineangiocardiography, surgery, or autopsy.

Cyanosis was present in all patients before 6 months of age. With 1 exception, all had cardiomegaly, and the majority had either continuous murmurs or separate systolic and diastolic murmurs at the base. Two infants did not have murmurs when first examined. The most frequent electrocardiographic feature was right ventricular or combined ventricular hypertrophy. P-wave anomalies of right atrial enlargement were found in 4 patients. Four others had normal tracings, including the oldest in the series. One patient had normal cardiac size and contour roentgenographically. The right ventricle was enlarged in all others, the left ventricle in 12, the left atrium in 11, and the right atrium in only 2. Hemodynamic studies and selective cineangiocardiography were performed in most of the patients. Three incorrect diagnoses were made: persistent atrioventricularis communis, aorticopulmonary septal defect or patent ductus arteriosus, and isolated ventricular septal defect. An end-to-end anastomosis of superior vena cava to right pulmonary artery was done in 3 patients with immediate development of superior caval obstruction. Another had a complete repair attempted with extracorporeal circulation. Three infants had pulmonary artery banding or tucking procedures. All operations resulted in death within a few hours except for 1 pulmonary artery tucking, performed quite recently, in a 4-month-old.

Six of the total group are living, with the longest follow-up 7 years. Postmortem findings were available in 10 cases.

Regulation of Breathing in "Heart Failure"

Bruce W. Armstrong, Robert T. Singleton, John M. Workman, and Nit Konsuwan, Baltimore, Maryland

Whenever the cardiac output of resting individuals in relation to O_2 consumption is reduced, either experimentally or by disease, the arterio-mixed venous O_2, CO_2, and pH differences must increase. Hyperpnea is another well-known concomitant of a subnormal resting cardiac output. Thus, the arterio-mixed venous differences and the ventilatory responses mimic the normal response to exercise. This suggests that if the mechanism responsible for regulating breathing during exercise were known, it might also account for the hyperpnea of an abnormally low cardiac output.

It has been shown that the hyperpnea of muscular exercise can be quantitatively accounted for by postulating that the body reacts to the pH and CO_2 tension of mixed venous blood in much the

same way as it reacts to the pH, CO_2 tension, and O_2 tension of arterial blood.

This concept has been applied to the patients with mitral stenosis, reported by Chapman et al. It enabled us to predict a mean ventilation during exercise of 69 L./min. preoperatively and 67 L./min. postoperatively; the observed values were 62 and 73 L./min., respectively. In persons with various forms of heart disease in whom we have measured arterial and mixed venous O_2, CO_2, and pH at cardiac catheterization, the concept also accounts quite satisfactorily for the ventilation at rest, recumbent and erect, and during treadmill exercise.

Effect of Sodium Intake on the Diuresis and Antidiuresis of a Benzothiadiazine

Mark L. Armstrong, Iowa City, Iowa

Thiazides are diuretic chiefly because sodium reabsorption is inhibited in the proximal tubules. Progressively higher sodium intakes lead to overload of sodium in the tubules, however, and the expected response to the diuretic is a decline to an imperceptible effect.

This problem was studied in the rat. Hydrochlorothiazide was given by gavage after stabilizing sodium balance at 4 levels by providing NaCl in drinking water as follows: A, 0 per cent; B, 0.9 per cent; C, 1.5 per cent; D, 2.0 per cent. At 24-hour intervals, body weight (BW), food consumption, fluid intake and volume, osmolality, sodium and potassium excretion of urine were measured.

The mean 24-hour urine volumes/100 Gm. BW for the control and post-thiazide periods were as follows for the 4 levels of sodium intake: A, 6.6 ml. → 20.9 ml. ($P < .001$); B, 10.5 ml. → 24.4 ml. ($P < .02$); C, 15.6 ml. → 13.9 ml. ($P < .05$); D, 42.3 ml. → 31.7 ml. ($P < .001$). The corresponding 24-hour values for sodium excretion/100 Gm. BW were as follows: A, 1.25 mEq. → 2.10 mEq. ($P < .001$); B, 4.24 mEq. → 7.38 mEq. ($P < .02$); C, 10.3 mEq. → 6.4 mEq. ($P < .02$); and D, 24.9 mEq. → 20.0 mEq. ($P < .01$).

Increasing oral salt loads not only attenuates but eventually reverses the diuretic effect of hydrochlorothiazide. These data, correlated with other studies, suggest that the action of a benzothiadiazine diuretic is approximately a sine function of the oral salt load given in this way, with the location of the descending null point (π intercept) at some position beyond 40 mEq. Na/Kg. BW.

Value of Blood Volume Determinations in Open-Heart Surgery

Safuh Attar, Joseph Workman, R. Adams Cowley, William G. Esmond, and Emil Blair, Baltimore, Maryland

Blood volume studies were done in 34 patients undergoing open-heart surgery using extracorporeal circulation with hypothermia. Plasma volume (PV) was measured directly by the isotope-dilution method, using iodinated human serum albumin. The total blood volume (TBV) was then calculated, using whole body hematocrit and the red cell mass (RCM) obtained by subtraction.

The determinations were done (1) prior to surgery, (2) 2 hours after surgery, (3) 18 hours after surgery, and (4) 1, 2, and 3 weeks after surgery. The preoperative mean values, compared to ideal estimated volumes, showed a hematocrit of 42 per cent, an increase of 16 cc./Kg. body weight of TBV, 10 cc./Kg. PV, and 6 cc./Kg. RCM. Determinations 2 hours after surgery showed no change in venous hematocrit, a decrease of 19 cc./Kg. of TBV, 12 cc./Kg. of PV, and 7 cc./Kg. RCM. The volumes measured 18 hours after surgery showed no change in hematocrit but an increase of 7 cc./Kg. in TBV, 5 cc. of which was due to an increase in PV. Determinations done 1, 2, and 3 weeks after surgery showed a definite decrease in hematocrit which was accounted for by hemodilution. The hematocrit dropped 6 per cent 1 week after surgery with an average increase of 12 cc./Kg. TBV, mostly due to PV expansion.

This preliminary study proves that conventional methods underestimate blood losses during open-heart surgery. In addition, no exact correlation was found between changes in blood volume and the changes in weight and arterial and venous pressure postoperatively.

Diagnostic Implications of Isozymes with Particular Reference to Myocardial and Pulmonary Infarction

Nuzhet O. Atuk, J. Edwin Wood, and Julian R. Beckwith, Charlottesville, Virginia

Although increased activity of plasma lactic dehydrogenase (LD) has been recognized as useful in the diagnosis of myocardial infarction, its occurrence in other disease states limits this usefulness. It has been suggested that electrophoretic separation and quantitative estimation of plasma LD isozymes permit identification of changes in the plasma LD activity pattern which specifically reflect myocardial infarction. Myocardial infarction is associated with an increase in plasma LD4 and LD5 with a preponderance of the latter, which is abundant in myocardium. The clinical significance of isozyme values in myocardial and pulmonary infarction has been reviewed.

Several isozyme determinations were made in plasmas from 12 patients who had chest pain. The values obtained from 20 normal individuals were used as controls. Six patients who had myocardial infarction showed increase in plasma LD5,

The increase in LD5 was detected within 10 hours and lasted 12 to 15 days following chest pain. Three patients with coronary insufficiency without myocardial necrosis showed no alteration in their plasma isozyme pattern. Plasma isozyme alterations in pulmonary infarction showed a sharp increase in LD3 and LD4 with relative elevation in LD5.

It is suggested that plasma isozyme estimation may provide a more specific method in diagnosing myocardial necrosis and may help in a differentiation of coronary insufficiency and pulmonary infarction.

Student Research as a Community Project

Marvin L. Auerback, John S. Blum, and Leo S. Bell, San Mateo, California

Four years ago, a grant-in-aid program was established for high school and junior college students in San Mateo County. Students were encouraged to amplify original ideas in the physical and biologic sciences in an experimental framework under the supervision of interested science teachers. The sole financial support of the program came from the San Mateo Heart Association, and students were selected by a committee representing the Heart Association and the county's high school science teachers. The experiments have encompassed a wide range of endeavor: from development of an apparatus to prevent air embolism during blood transfusion, to the physics of cake baking by a girl who wanted the scientific reason for a cake's rising, to the development of a computer capable of solving 3 linear equations simultaneously. As a result of the program, 83 students learned for the first time the difficult mechanics of originating, budgeting, and recording experiments, of using controls, and of observing results which sometimes differ surprisingly from those which are anticipated. They were introduced to the technic of reporting these results at research meetings and of answering the questions of fellow students and instructors. It is hoped that other Heart Association chapters will be encouraged to assume responsibility for interesting gifted young people in research.

Dextrorotation of the Heart: Angiocardiographic Study of Seventeen Cases

Stephen M. Ayres and Israel Steinberg, New York, New York

Dextrorotation (DR) probably results from arrest of the leftward and clockwise rotation occurring in the sixth week of fetal life. Unlike mirror image dextrocardia (MID), which results from a complete reversal in laterality of both thoracic and abdominal viscera, the chambers are normally arranged in DR. Angiocardiography demonstrates clockwise and rightward rotation of the heart. Both ventricles are anterior and parallel to one another with the atria directly posterior. The pulmonary artery is more medial than normal, but the anterior-posterior orientation of the great vessels is normal in uncomplicated cases. The electrocardiogram provides clear differentiation from MID. The ÂP ranged from −75 to 90 degrees; ÂQRS from 0 to 255 degrees. The QRS-T angle was greater than 90 degrees in 5 patients.

Cardiac anomalies were present in 14 patients and included transposition of the great vessels in 5, anomalies of atrial and ventricular septa in 5, and anomalous drainage of the right pulmonary veins into the inferior vena cava in 4. The manubrium sterni was absent in 1, and there was eventration of the right diaphragm in 2 and of the left diaphragm in 1. These indicate that DR results from a teratogenic agent acting during the sixth week, the period during which septation and conotruncal division occur. The eventration of the diaphragm is not a cause of DR but an associated anomaly, since differentiation of the septum transversum also begins at this time. Angiocardiography is valuable for diagnosis of associated significant anomalies.

Treatment of Hypertension with Alpha Methyl Dopa

Benjamin H. Barbour and Max H. Weil, Los Angeles, California

Alpha methyl dihydroxyphenylalanine (α-MDOPA), a structural analog of dihydroxyphenylalanine (DOPA), competitively inhibits decarboxylase and lowers blood pressure in the intact animal, presumably by blockage of norepinephrine synthesis. Eleven patients were observed for 5 days prior to therapy, 10 days while receiving α-MDOPA, and 5 days after therapy. No treatment had been used for 2 weeks prior to the study. Nine patients received 3.0 Gm. daily of dl-α-MDOPA, and 2 patients received 1.5 Gm. daily of l-α-MDOPA.

Pretreatment blood pressure was 178 ± 2.9 mm. (standard error of mean) systolic and 112 ± 1.8 mm. diastolic supine and 161 ± 2.7 systolic and 117 ± 1.9 diastolic standing. During treatment, blood pressures fell to 153 ± 1.6 systolic and 95 ± 1.2 diastolic supine and to 120 ± 1.8 systolic and 85 ± 1.2 diastolic standing. The difference between the control and treatment periods was significant in the supine and standing positions ($P < 0.0001$). Although the blood pressures re-

turned toward pretreatment levels, a significant reduction was observed during the 5 days following therapy: 162 ± 2.1 systolic and 97 ± 1.3 diastolic supine and 149 ± 3 systolic and 101 ± 1.7 diastolic standing.

Liver function tests, white blood counts, and blood urea nitrogen remained unchanged. Renal clearance of para-aminohippuric acid (Cl_{PAH}) and creatinine (Cl_{cr}) was measured in 7 patients before, during, and after therapy. Cl_{PAH} was 398 ± 51 ml./min., 384 ± 63, 409 ± 56 during the control, treatment, and post-treatment periods, respectively. The Cl_{cr} was 68 ± 8 ml./min., 93 ± 12 ml./min., and 78 ± 8 during the control, treatment, and post-treatment periods, respectively. Inexplicably, the hemoglobin fell in 4 patients.

These results suggest that this agent produces a fall in blood pressure with little change in renal hemodynamics.

Use of an Electrode for Continuously Recording Intracardiac pO_2 Changes in Cardiac Catheterizations (P)

Lionel M. Bargeron, Jr., Leland C. Clark, Jr., and Champ Lyons, Birmingham, Alabama

Previously, we described a potentiometric hydrogen-sensitive electrode, consisting of a platinized platinum bead mounted on the tip of a cardiac catheter, which has proved useful in the detection of left-to-right shunts. We have investigated an alternative use of this electrode as an oxygen-sensitive device to record continuously the changes in pO_2 throughout the heart and great vessels. An increase in pO_2 causes a change in potential opposite in polarity to that produced by an increase in pH_2, probably according to the reaction: $2\ H_2O \leftarrow + 4H + \rightleftarrows 2H_2$. The location of the electrode tip in the heart is verified by the intracardiac electrocardiogram tracing, which is simultaneously recorded from the electrode and by pressure measurements taken through a lumen in the catheter. By observing the potential of the electrode as the catheter is advanced, it is often possible to trace a stream of oxygenated blood to its source in a defect. Even renal and hepatic venous blood can be located as it streams into the vena cava. Detection of such streams or of oxygenated chambers can be accomplished while the patient is breathing air but is facilitated by oxygen breathing. In the latter situation, potential changes traversing the full span of the oscillograph (100 mv.) are observed as the electrode passes into an arteriovenous shunt. Verification of a left-to-right shunt is done by single-breath hydrogen tests using the same electrode catheter.

Cardiovascular-Respiratory Actions of Mephentermine in Mitral Stenosis and Its Effects on Pulmonary Function in Chronic Pulmonary Emphysema

Frank Barrera, Morton J. Oppenheimer, Philadelphia, Pennsylvania, Gabriel Regalado, Rosa L. Changsut, and Jose C. Dominguez, Havana, Cuba

Mephentermine increases maximum breathing capacity in emphysema patients due to partial relief of existing bronchospasm. Small variations occur in tidal volume, arterial blood saturation, O_2 uptake, and CO_2 removal per L. ventilation and in respiratory quotient. There is an increase in expiratory minute volume, alveolar ventilation, frequency of respiration; a decrease in physiologic dead space, physiologic dead space/tidal volume ratio, CO_2 content and tension in arterial blood; and an increase in O_2 consumption, CO_2 elimination, and arterial blood pH. These changes are marked in normal individuals and in mitral stenosis patients, in contrast with the minimal effects obtained in emphysema cases. Pulmonary and circulatory effects suggest that mephentermine affects ventilation-perfusion relationships throughout the lung. The disproportionate increase in ventilation and frequency of respiration with hypocapnia and alkalosis suggest an important central effect. In normal and in mitral stenosis patients, mephentermine produces an increase in heart rate, decrease in mean right atrial pressure, and an increase in cardiac output as a result of myocardial stimulation. Pulmonary arteriolar resistance decreased in the majority of cases, while wedge pressures increased or decreased very slightly. These changes are interpreted as pulmonary vasodilatation. Increased cardiac output, falling systemic resistances, and decreased A-V O_2 differences suggest an increase in peripheral blood flow with vasodilatation. The fact that systemic resistance increased slightly in some cases must mean that vasoconstriction with decreased peripheral blood flow occurred in other vascular beds as a compensatory reaction.

Prevalence of Atherosclerotic Complications in Trappist and Benedictine Monks (P)

J. Gordon Barrow, Atlanta, Georgia, Carroll B. Quinlan, Boston, Massachusetts, Robert E. Edmands, and Philip T. Rodilosso, Atlanta, Georgia

A medical history was obtained and a physical examination, including an electrocardiogram, was performed on each of 684 Trappist monks (28 per cent calories from fat) and 1253 omnivorous Benedictine monks (47 per cent calories from fat) in order to assess the prevalence of atherosclerotic complications in these age-comparable groups.

Historical evidence of myocardial infarction or

angina pectoris was obtained from 23 Benedictine and 3 Trappist monks, while physical examination disclosed evidence of peripheral arterial occlusion in 1 Benedictine and 0 Trappist. Unequivocal electrocardiographic changes, according to the criteria of Keys et al., were recorded by 3 observers as follows: (1) QRS changes (myocardial infarctions): 10 Benedictines, 0 Trappist. (2) Nonspecific ST-T changes: 28 Benedictines, 13 Trappists. (3) A-V conduction disturbances: 12 Benedictines, 0 Trappist. (4) Atrial arrhythmias: 2 Benedictines, 4 Trappists.

In summary, 26 Benedictines (2.1 per cent) and 3 Trappists (0.4 per cent) were found with historical, physical, or electrocardiographic (QRS) evidence of atherosclerotic complications. An additional 36 Benedictines (2.9 per cent) and 14 Trappists (2.0 per cent) demonstrated nonspecific electrocardiographic abnormalities (groups 2, 3, and 4 above).

While the above findings are inconclusive as to the relative incidence of atherosclerotic complications in the 2 study groups, a difference in prevalence is certainly suggested. In view of the marked disparity in diets and average serum lipids (Benedictine cholesterol—232 mg. per 100 ml.; Trappist cholesterol—208 mg. per 100 ml.), these data indicate the need for further study.

Clinical Significance of Nonbacterial Endocarditis

William E. Barry and Dante Scarpelli, Columbus, Ohio

Twenty-one cases of nonbacterial thrombotic endocarditis (marantic of terminal endocarditis) over a 12-year period were reviewed from pathologic material and retrospectively studied for clinical details, with particular reference to the occurrence of embolic phenomena and the possibility of antemortem diagnosis.

Histochemical and morphologic studies, including electron microscopy of the valve vegetations, demonstrated identity of the lesions with vascular thrombi employed as fibrin controls. Swollen collagen fibers were present at the base of the vegetations in all instances and suggested both degenerative and thrombotic factors in the genesis of marantic endocarditis.

Metastatic malignant diseases were present in over half the cases. The majority of the remainder had stressful conditions, such as perforated ulcer, ruptured aneurysm, and bleeding gastric ulcer. Gross and microscopic infarcts in kidney, spleen, and brain were demonstrated in 9 of 21 cases. In a control group of 50 cases of metastatic malignancy, infarcts occurred in 7 instances ($P < .01$). In 4 of 13 cases, clinical episodes occurred which were consistent with embolic phenomena but were not recognized as such antemortem. These included splenic infarction and cerebral vascular accidents, the latter possibly causally related to death. The presence of cardiac murmurs was inconstant and is not surprising because of the bland nondestructive nature of the vegetations. Thus, it is doubtful that auscultation would be helpful in clinical diagnosis. However, one might suspect this entity to be present in debilitating diseases when infarctions occur in various organs.

Left Ventricular Volume in Patients with Giant Left Atrium

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In a previous comparative study, the mean horizontal angle of the resultant QRS vector in 19 patients with giant left atrium (–48.2 degrees) was statistically similar to the mean angle of 21 patients with left heart failure (–52.7 degrees) but with a smaller magnitude, suggesting enlarged left ventricles in patients with giant atria.

Left ventricular volume was calculated in 6 additional patients with massive mitral insufficiency (group I) and in 3 normal controls (group II), using the biplane cineangiofluorographic method and a modification of Arvidsson's technic. End-diastolic and end-systolic phases of the left ventricular cycle (AP and left lateral) were measured. Left atrial volumes were similarly calculated.

Left atrial volume averaged 465 ml. (251 to 780 ml.). End-diastolic and end-systolic left ventricular volumes averaged 197 ml. (116 to 271 ml.) and 50 ml. (25 to 83 ml.), respectively, as compared to average normal volumes of 102 and 39 ml., respectively.

The mean thickness of left ventricular wall during diastole in groups I and II was not significantly different, although the average value in group I was slightly higher than that in group II.

Left ventricular enlargement is thus frequently seen alongside massive mitral insufficiency. The nature of this enlargement remains problematic. Volume data and vector analysis confirm enlargement rather than hypertrophy. While some degree of hypertrophy may be present, the problem can best be resolved by placing the emphasis on dilatation rather than true hypertrophy, unless a complicating lesion is present.

Intestinal Fat Absorption in Idiopathic Hyperlipemia (P)

David R. Bassett and Peter T. Kuo, Philadelphia, Pennsylvania*

Recent studies of the serum chylomicron fatty acid pattern of patients with idiopathic hyper-

lipemia suggest the presence of abnormal intestinal fat absorption. Investigations were undertaken to delineate further the mechanism involved. Radioactive triolein was administered orally, intravenously, and intraduodenally to 5 patients with idiopathic hyperlipemia, 5 with familial hypercholesterolemia, and 5 young nonlipemic subjects.

In comparative studies of normal and hypercholesterolemic subjects, the respective pairs of blood radioactivity curves were alike, whether the triolein-I^{131} was given orally, intravenously, or by intraduodenal infusion. When fat emulsion labeled with triolein-I^{131} was administered rapidly into the duodenum (at 3 ml./min.) in these 2 groups, much of the fat was not absorbed, as indicated by a marked increase in fecal radioactivity.

In hyperlipemic subjects, the blood radioactivity curves following oral triolein showed a rise to high levels following absorption and a delayed disappearance of radioactivity, which was directly related to the severity of the lipemia and improved with control of the lipemia. If the factor of an increased serum lipid pool in these subjects is taken into consideration, their blood radioactivity disappearance curves following intravenous triolein were essentially normal. Following rapid intraduodenal infusion of fat emulsion, the blood radioactivity of hyperlipemic patients rose to a high level, with little increase in their fecal radioactivity excretion. The low fecal fat excretion following rapid intraduodenal fat administration in hyperlipemics was confirmed by quantitative (chemical) and qualitative (chromatographic) fecal analyses.

Thus, a rapid and intensified fat absorption mechanism is demonstrated in these patients with idiopathic hyperlipemia.

Optical Densitometric Behavior of Sodium Acetrizoate-Indocyanine Green-Whole Blood Mixtures

Edward J. Battersby, Ronald H. Fishbein, Robert J. Wilder, and Mark M. Ravitch, Baltimore, Maryland.

The effects of sodium acetrizoate on the optical density of blood and the measurement of indocyanine green concentrations in sodium acetrizoate-blood mixtures were studied both in constant mixtures and in a circulatory model.

When 70 per cent sodium acetrizoate is added to whole blood, plotting the volumes per cent of sodium acetrizoate against optical density produces a diphasic curve with an increase in optical density up to approximately 25 volumes per cent of sodium acetrizoate and a decrease in optical density thereafter. These measurements, performed in a standard interference filter densitometer, result in similar curves both at 6,400 and 8,000 Å. When a sodium acetrizoate-indocyanine green mixture is added to whole blood, indocyanine green dye concentration plotted against optical density at 8,000 Å produces a nonlinear curve. Since sodium acetrizoate in whole blood gives similar optical response at both 6,400 and 8,000 Å and since indocyanine green in blood has an insignificant response at 6,400 Å, subtracting the optical density changes at 6,400 Å from those at 8,000 Å results in a linear curve up to 15 mg. of indocyanine green per L. of mixture.

Output studies in a circulatory model using a sodium acetrizoate-indocyanine green mixture as described above were performed. If low concentrations of sodium acetrizoate were employed, using 2 densitometers and subtracting the optical density changes at 6,400 from those at 8,000 Å, the accuracy of the output measurement was not greater than with the use of a single densitometer at 8,000 Å. The nonlinear response at 8,000 Å, however, apparently introduces significant error at higher concentrations of sodium acetrizoate and may also do so in determinations where step functions are measured, i.e., diastolic volume determinations.

Effect of Pulmonary Emphysema on Cardiopulmonary Hemodynamics at Rest and During Exercise

Roy H. Behnke, Douglas H. White, and John F. Williams, Jr.,† Indianapolis, Indiana

To clarify further the variation in resting cardiopulmonary hemodynamics in patients with pulmonary emphysema and to define the changes in dynamics effected by exertion, 53 such patients were studied at rest and 44 patients during exercise. The diagnosis of pulmonary emphysema was made from clinical data, roentgenograms, and pulmonary function tests. All hemodynamic data were obtained by right-heart catheterization, supine and in a compensated cardiac state. The patients were divided into 2 groups: 33 subjects with no history of right ventricular failure and 20 subjects who had been in failure.

No subject had an increased cardiac index at rest, and the mean index was below that of normal man, and to a greater degree in failure subjects. Those with a history of failure were unable to effect an increase in exercise cardiac output proportionate to oxygen consumption; the nonfailure subject response was normal. An increased A-V oxygen difference was the primary factor responsible for the decreased indices in both groups. The mean pulmonary artery pressure was elevated at rest and excessively increased by exercise in both groups, again more in the failure patients. While both groups had an elevated pulmonary vascular resistance at rest, this value rose sharply with exercise in those with failure but remained unchanged in those without failure.

It appears that although subjects with pulmonary emphysema who have not been in right ventricular failure may have demonstrable abnormalities in their cardiopulmonary hemodynamics at rest, the response to exercise of their cardiac output and pulmonary vascular resistance is comparable to that in normal subjects during similar degrees of exertion. Once a subject has had failure, definite exercise abnormalities of these parameters persist in the compensated cardiac state.

Direct Action of Acetylcholine and Norepinephrine on the Pulmonary Vascular Bed Demonstrated by Perfusion Studies of the Wedged Segment

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Controlled perfusion through a properly wedged catheter in the intact animal assures both constant flow and preservation of physiologic reflexes. In 25 intact anesthetized dogs, a number 10 thin-walled catheter was wedged in a distal pulmonary artery and perfused with precisely determined flows of heparinized autologous blood from an infusion syringe. Femoral artery (FA) pressure, perfusion pressure in the wedged segment (WPP), and left atrial (LA) pressure directly measured or reflected in the pulmonary capillary wedged pressure were monitored.

The pressure-flow relation of the perfused wedged segment was studied by perfusing flows of 0.5 to 100 ml./min. At low flow rates, flow increases yield greater pressure increments than at high flow rates, producing a curve convex to the flow axis. This wedged perfusion curve is similar to those derived by others for total lung perfusions.

Acetylcholine (ACH), 0.5 to 50 μg. introduced into the perfused segment, induced an immediate increase in WPP before any change in LA or FA pressure, heart rate, or respiration. With the smaller doses, increase in WPP was demonstrated without measurable change in these latter variables. Norepinephrine 1 to 5μg. produced a dose-related increase in WPP, again prior to alteration of other measured variables.

Since the increased pressure response occurs independently of changes in FA and LA pressure, heart rate, and respiration and since flow through the perfused segment is precisely controlled, a direct vasomotor action by these drugs on the pulmonary blood vessels is demonstrated.

Electrocardiogram During Exercise as Recorded by Radioelectrocardiography: Comparison with the Postexercise Electrocardiogram (Master 2-Step Test) (P)

Samuel Bellet, Stavros Deliyiannis, and Marcel Eliakim, Philadelphia, Pennsylvania

Hitherto, the evaluation of the effect of exercise on the electrocardiogram has been limited chiefly to observations during the immediate postexercise period. A new radioelectrocardiography system, permitting recording close to or at a distance of several hundred feet from the patient, was employed in this study. This system made possible the recording of electrocardiograms during various types of exercise, without interference and with a stable baseline. The electrocardiogram during and after the Master 2-step test was examined in 127 normal subjects and 147 patients with hypertensive-arteriosclerotic cardiovascular disease, including 38 patients with coronary insufficiency. In the patients with hypertensive-arteriosclerotic cardiovascular disease, the abnormalities observed during exercise consisted of ischemic S-T depression, T-wave inversion, elevation of a previously depressed S-T segment, and reversion of a negative T wave to an upright position. These alterations were found only or chiefly during exercise in 58 per cent, only or chiefly after exercise in 20 per cent, and equally during and after exercise in 22 per cent of patients who showed abnormal responses. This finding is considered to be highly significant in view of the importance of the electrocardiogram in the detection of myocardial disease.

It is concluded that the electrocardiogram during exercise is an extremely valuable adjunct in the detection of myocardial disease. The information obtained during this period of exercise is often unavailable or inadequately shown in the postexercise period. These findings are in harmony with the fact that the maximal stress on the heart occurs during the period of exercise. The "exercise test," therefore, should supplement the presently used technic in the performance of the Master 2-step test.

Apexcardiogram in Ischemic Heart Disease; Effect of Exercise and Nitroglycerin on the Atrial Contraction

Alberto Benchimol and E. Grey Dimond, La Jolla, California

The apexcardiogram (recording of the movement of the chest wall overlying the left ventricle) was recorded, using a pulse wave crystal microphone in 35 cases of arteriosclerotic heart disease and 34 normal subjects. The influence of exercise and nitroglycerin on the apexcardiogram was studied in 18 cases of arteriosclerotic heart disease and in 20 control subjects.

The apexcardiographic waves corresponding to ventricular filling due to atrial contraction ("a" wave) and ventricular ejection (systolic wave) were analyzed.

In normal subjects at rest, the amplitude of the "a" wave, expressed as a percentage ratio of the

total amplitude of the systolic wave, ranged from 2 to 15 per cent (average 11 per cent). In the group with ischemic heart disease, it ranged from 13 to 61 per cent (average 28 per cent). There was an overlap of 8 per cent in the abnormal group and 2 per cent in the normal.

Exercise (double Master 2-step) produced an average 2-fold increase in the amplitude of the "a" wave in coronary artery disease patients and insignificant or no increase in normal subjects.

Nitroglycerin given after exercise to patients with arteriosclerotic heart disease produced complete disappearance of the "a" wave in 11 (61 per cent) and significant decrease in amplitude in 7 cases (39 per cent).

In 5 cases, nitroglycerin administered before exercise prevented the appearance of the abnormal postexercise "a" wave.

These studies indicated an abnormal ventricular filling due to atrial contraction in patients with coronary artery disease. The apexcardiogram seems to be a sensitive method to detect this abnormal physiologic event.

Experimental Measurement of Myocardial Blood Flow with Radioactive Sodium Chloride

Bernard Bercu, Luis Ruiz, Joseph A. Smith, and Ina Fechner, Eloise, Michigan

Kety first showed in 1949 that the rate of disappearance of a small depot of radioactive sodium in a tissue was a measure of the local blood flow in that tissue. This principle has recently been applied to the myocardium by the authors and other investigators. However, the myocardial blood flow is sufficiently rapid that a small depot of radioactive sodium in the myocardium will disappear before an accurate slope of its rate of fall can be recorded. This precludes the use of a direct measurement of the disappearance curve of radioactive sodium for an accurate measurement of myocardial blood flow. An alternate method has been developed which permits a more accurate measurement of coronary blood flow.

Mongrel dogs were used for this study. Left coronary artery blood flow was measured by perfusing it with blood passed through a recording flowmeter. Approximately 20 μc. of radioactive $Na^{24}Cl$ in a volume of 0.1 ml. were injected into the left ventricular myocardium. Blood from the pulmonary artery was drawn through a scintillation counter with a constant drawing syringe to measure a radioactive dilution curve. The shape of this curve depends on cardiac output, the quantity of radioactive $Na^{24}Cl$ injected, and the rate of entry of the radioactive $Na^{24}Cl$ from the myocardium into the blood. Cardiac output was measured with a separate curve, so that the rate of entry of radioactive $Na^{24}Cl$ into the blood or, conversely, its disappearance from the myocardium could be calculated. This value was then used to determine myocardial blood flow.

Use of Aortic Constriction to Increase Coronary Blood Flow

Bernard Bercu, Luis Ruiz, Joseph A. Smith, and Ina Fechner, Eloise, Michigan

It has been observed for some time that in congenital supravalvular aortic stenosis, the coronary arteries become extremely dilated. This observation raised the possibility that mild supravalvular aortic stenosis might increase the perfusion pressure and flow in the coronary arteries without an equal increase in myocardial oxygen consumption. Since individuals with aortic valvular stenosis tolerate pressure gradients as high as 60 mm. Hg across the aortic valve, it seemed likely that a similar degree of supravalvular aortic constriction might also be well tolerated.

Ten dogs were subjected to constriction of the ascending aorta, and acute changes in cardiovascular hemodynamics were measured. Ten other dogs were allowed to survive aortic constriction for at least 6 months before they were studied.

Arterial pressures were measured with a Statham strain gauge manometer. Cardiac output was measured by the dye-dilution technic. Coronary blood flow was estimated by measuring coronary sinus flow. Blood oxygen saturations were measured with a cuvette oximeter.

In the acute experiments, coronary blood flow increased in proportion to the degree of aortic constriction. With mild degrees of aortic constriction, coronary blood flow increased approximately 20 per cent. However, in this group of animals, myocardial oxygen consumption and myocardial work increased in proportion to coronary blood flow. In the chronic experiments, where the heart was permitted to adjust to the systolic pressure load, the increase in coronary blood flow was greater than the increase in myocardial oxygen consumption. Anatomic studies revealed no significant changes in the coronary arteries.

Malabsorption as a Complication of Congestive Heart Failure

Donald Berkowitz, Millard W. Croll, and Bernard Shapiro, Philadelphia, Pennsylvania

The recent availability of radioactive-tagged lipids has made it possible to study and detect the presence of impaired fat absorption in a much simpler manner than heretofore. The present study is an extension of these technics in a group of patients with congestive heart failure in an attempt to determine the frequency of malabsorption.

Twenty-five subjects with gross evidence of right-sided heart failure were given a test meal of radioactive-iodinated triolein, following which serial blood samples were taken during the next 24 hours and stools collected for 48 hours. The amount of radioactivity in each specimen was determined and expressed as a percentage of the initially ingested fat.

Over 50 per cent of the group showed definite impairment of absorption of the radiotriolein, as demonstrated by lower than normal postprandial blood radioactivity levels and correspondingly higher than normal fecal radioactivity. The degree of impairment appeared to be related to the severity of the heart failure. Repeat studies after restoration of compensation invariably showed improvement in the amount of fat absorbed.

In 5 of the patients with evidence of decreased I^{131}-triolein absorption, I^{131}-oleic acid absorption was also measured. In 2, it was markedly impaired. This suggests that both a digestive and an absorptive defect may play a role in the faulty lipid digestion seen in these individuals, perhaps as a result of congestion and edema of the pancreatic acini and the intestinal mucosa.

The present data thus indicate that dietary fat is frequently poorly absorbed in patients with congestive heart failure and may explain some of the weight loss and malnutrition commonly associated with this condition.

Evaluation of a New Pulse-Contour Method for the Examination of Cardiac Output

Eugene F. Bernstein and Robert L. Evans, Minneapolis, Minnesota

Currently available technics for the measurement and estimation of cardiac output in both experimental laboratory and clinical situations involve difficult catheterization, sampling, and analytic technics. Furthermore, they offer essentially averaged cardiac output data over 30-second to 2-minute periods. A pulse-contour method, based on a single propagated pulse wave and on conversion of pressure terms to those of velocity, has recently been proposed by Evans and is experimentally evaluated in this study.

In 14 dogs, almost simultaneous measurements of cardiac output were made with dye-dilution, direct Fick, and this pulse-contour method. Measurements were obtained in both closed- and open-chest preparations with a wide variety of blood pressures and physiologic states.

In 84 almost simultaneous dye-dilution and pulse-contour comparisons, there was a deviation of 14.0 ±27.0 per cent. In 22 direct Fick and pulse-contour comparisons, there was a deviation of 19.1 ±32.6 per cent. The direct Fick measurements varied from almost simultaneous dye-dilution studies by 8.1 ±15.7 per cent. These data and others to be presented show that the pulse contour (1) varies about twice as much as the other 2 methods, (2) gives good beat-to-beat absolute values, and (3) follows almost all relative changes of the kind tested.

This technic involves a single arterial catheterization and permits beat-to-beat quantitation of relative changes in cardiac output. It offers a simple and usefully accurate tool for the study of cardiac output in both the experimental laboratory and clinical situations. Only simple arithmetic computation is required.

Alterations of Serum Proteins in Acute Rheumatic Fever (P)

Stanley H. Bernstein and Jona Allerhand, New Hyde Park, New York

Investigation of the serum proteins of patients with acute rheumatic fever by paper electrophoresis has revealed distinct and consistent changes in the globulin patterns. Other investigators have found the changes in these fractions to be inconsistent and apparently dependent on the time in the rheumatic state at which the samples were obtained. These discrepancies required further elucidation. Sera of 35 patients, fulfilling the criteria for active rheumatic fever, were drawn during the first week of clinical illness and during convalescence. Thirty-five patients with acute streptococcal infections were used as controls. Twenty-five rheumatic patients were in their initial attack, while the remainder evinced recurrent activity. All rheumatic sera during the first week of illness showed elevations of alpha 2 and gamma globulin. This pattern was independent of the major site of rheumatic involvement. The height of the globulin peaks was not related to the clinical severity of the disease. In comparing this pattern with that of patients with streptococcal infections, only the gamma globulin increases were common to both groups and only in instances when ASO titers were comparably elevated. The data suggest that alpha 2 and gamma globulins of acute phase sera in rheumatic fever are both invariably elevated and that this fact may be a guide to the activity of the disease. The gamma globulin elevations appear to be related to streptococcal antibody response, while the alpha 2 appears to reflect the tissue injury. In an attempt to characterize these globulin changes further, immunoelectrophoresis, using normal human antisera as well as antisera obtained from rabbits immunized with the rheumatic sera, are presently being carried out.

Relationship Between Venous Pressure and the Formation of Edema

Albert G. Bickelmann, James E. Lasry, and Eugene J. Lippschutz, Buffalo, New York

The authors have had the opportunity to study serial changes (5 individual studies) in cardiac output (dye-dilutional method) and peripheral vascular pressures in a patient with complete heart block whose cardiac rate was fixed at 60 beats per minute by implantation of an internal cardiac pacemaker.

Preoperatively, the patient had a cardiac rate of 43 beats per minute, associated with a stroke volume of 120 ml., a cardiac index of 2.90 L./min./M.^{2} (normal 2.5 to 4.5 L./min./M.^{2}), and a normal venous pressure. Although the patient was asymptomatic at rest, mild activity precipitated attacks of acute pulmonary edema on 2 occasions.

Two weeks after pacemaker implantation, the studies demonstrated an abnormally low cardiac index (1.80 L./min./M.^{2}), pulsus alternans, and a normal venous pressure. One week later, a slight rise in cardiac index had occurred (2.10 L./min./M.^{2}) but was associated with venous hypertension and rapidly developing edema. The patient was then digitalized for the first time, maintained on an unrestricted sodium intake, and did not receive diuretics. Subsequent study revealed that a normal cardiac output had been achieved, and although venous pressure had decreased, it was still abnormally high. Diuresis was delayed until the venous pressure had returned to normal limits.

The study demonstrates the beneficial effects of digitalis on myocardial contractility independent of cardiac rate. The retention and diuresis of sodium and water in this individual appeared to be related to changes in venous pressure rather than to cardiac output.

Open Cardioangiography

Aydin M. Bilgutay, Minneapolis, Minnesota

Advances in cardiovascular surgery demand equal progress in cardiovascular radiology to keep pace. A wide variety of defects of the heart and great vessels can be identified and evaluated preoperatively with precision by existing technics. The surgeon thus equipped with intimate knowledge of the anatomic defect and physiologic malfunction preoperatively is much better prepared to deal with it successfully. Nonetheless, certain unexpected and unanticipated conditions may be encountered at the time of surgery which may demand further identification. Also, an immediate postoperative and objective evaluation of the completeness of correction with the patient still on the table can be of great value in reducing postoperative mortality in some cases and in obviating the need for reoperation in others.

"Open" cardioangiography consists of obtaining films on the table of operative sites after introduction of radiopaque material selectively. Valuable information is thereby gained, and the procedure has been found technically feasible and safe. This method of operative or "open" angiography has been applied to aortic and mitral valves, right and left ventriculography, pulmonary angiography, and coronary angiography. A suitable technic has been evolved for each of these sites. The feasibility of clinical application of these technics has been demonstrated in connection with surgery on aortic, mitral, and pulmonary valves and in coronary artery disease. It is believed that "open" cardioangiography will prove to be a useful addition to the armamentarium of the heart surgeon.

Relationship of Resting and Postexercise Electrocardiographic Abnormalities to Obesity, Hypertension, and Hypercholesteremia in Working Men

Henry W. Blackburn, Henry L. Taylor, Minneapolis, Minnesota, Thomas C. Puchner, Milwaukee, Wisconsin, and Ancel Keys, Minneapolis, Minnesota

Clinically interesting relationships between certain electrocardiographic abnormalities and measurable physical characteristics of men appeared in systematic studies of working populations. Electrocardiographic findings were analyzed among 1,646 clerks and switchmen ages 40 through 59 years within a study of heart disease among railroad employees. The observed frequency of electrocardiographic items was tabulated according to clearly defined common clinical criteria and compared to the expected frequency calculated on the basis of assumption of an equal distribution of abnormalities between subjects with high and lower relative weight ($\geq$ 110 per cent), fatness ($\geq$ 40 mm. average sum of 2 skinfolds), systolic ($\geq$ 160 mm. Hg) and diastolic ($\geq$ 95 mm. Hg) blood pressure, and serum cholesterol ($\geq$ 260 mg. per 100 ml.).

No significant relationship was found between an objective category of large Q waves and any of these characteristics, but the total number of clear old infarct cases was small (21 of 1,646).

T-wave negativity of –1 mm. or more (any of leads I, II, aVL, V_2 to V_6) was significantly more common in the hypertensive subjects. Marked left

axis (over –30 degrees) was unrelated to obesity, hypertension, or hypercholesteremia in this United States working group. Left "hypertrophy" (by common amplitude criteria) was found in excess among those with elevated blood pressure. Post-exercise S-T depression (—1 mm. junction or flat or sagging segment) was found in 114 men, significantly more among the obese and hypertensive and in the sedentary occupational class, but not more in the hypercholesteremic. Consideration is given to the question whether "positive" exercise tests in otherwise "healthy" men are specific for coronary insufficiency or rather are a nonspecific reflection of functional cardiovascular status. Evidence is available that the interrelationship between electrocardiographic abnormalities and physical characteristics of men may differ in other countries and cultures.

Study of the No-Flow Reflex Bradycardia

Emil Blair, Juanito Roa, Safuh Attar, and R. Adams Cowley, Baltimore, Maryland

When blood flow is completely stopped, 2 cardiac events have been observed: (1) a tachycardia, coincident with the fall in arterial blood pressure and mediated by carotid and aortic baroceptors, and (2) a bradycardia, mechanism unknown. No-flow was produced by total inflow circulatory occlusion in open-heart, pentobarbitalized dogs on room air IPPB. The bradycardia appeared after 2.5 minutes of no-flow. In 1 group of studies, the occlusion was terminated at 3 minutes to permit observation of release phenomena. In another group, occlusion was continued. The bradycardia lasted an average of 40 seconds, terminating abruptly ("vagal release"). Administration of atropine or bilateral vagectomy before no-flow abolished the bradycardia. Denervation of the carotid and aortic baroceptors and vasomotor alteration had no effect. Moderate hypothermia (28 to 30 C.) abolished the reflex. In another group, O_2 content dropped, CO_2 was unchanged, HCO_3^- dropped, lactic acid rose, and pH fell. Thus, hypoxemia (with subsequent metabolic acidosis) appeared to be a unit in the mechanism for the bradycardia and suggested a possible chemoceptor role somewhere. Oxygenated blood was perfused into the coronaries during no-flow. The bradycardia persisted, ruling out an oxygen-dependent cardiac chemoceptor. Perfusion of the brain with oxygenated blood via the carotid arteries during no-flow abolished the bradycardia. The mechanism of the no-flow bradycardia has not been elucidated. It is mediated by increased vagal activity. It appears that a chemoceptor feedback system is involved, identity of which is unestablished, although the role of a pressoreceptor has not been ruled out.

Morphologic Study of Inherent Revascularization Following Experimental Myocardial Infarction

Emil Blair, Juanito Roa, and R. Adams Cowley, Baltimore, Maryland

According to Mallory and coworkers, ingrowth of blood vessels in the human infarcted heart is limited. Karsner and Dwyer in 1916 described histologic changes of infarction and healing in experimental acute coronary ligation in the dog. No specific note was made of the inherent revascularization. The present study was undertaken with emphasis on (1) time of appearance of vascularity, (2) extent and size of the new blood vessels, (3) period of maximal vascularity, and (4) period of devascularization. Infarcts were produced in dogs by the spiral Al-Mg alloy wire technic. The alloy permits a gradual occlusion, presumably encouraging vascular response to injury. Studies were done at regular intervals over a period of 3 months. On the fourth day, beginning at the periphery and extending throughout the injured area, capillaries appeared and then larger vessels to small-sized arteries around 3 to 4 weeks. Maximum vascularity was reached in the fourth week. The course of collagen and fibroblastic activity paralleled the developing revascularization, then continued as the vascularity noticeably diminished by the fifth to sixth week. After this time, evidence of contracture appeared. By the second month devascularization was almost complete, and the scar approached maturity. Within the third month the scar was contracted markedly.

Profuse vascular ingrowth, as observed in the normal dog's heart, suggests the requirement of a relatively uncompromised source of blood flow. In the human, the inherent revascularization appears to be limited, the compromise probably being due to arteriosclerosis.

Vectorcardiography in Uncomplicated Canine Bundle-Branch Block

David F. Blake and Paul Kezdi, Chicago, Illinois

In dogs under Nembutal anesthesia, open cardiotomy was performed, and Dacron fibers were looped beneath the right bundle branch (7 dogs), over the left bundle branch (3 dogs), and about both (1 dog). Tension on these suture ends produced transient, complete bundle-branch block. The sutures were then led from the right atriotomy wound for burial beneath the thoracic dermis. After recovery, tetrahedral vectorcardiograms were

recorded in the conscious and closed-chest state, before and after right or left bundle-branch block, with the dog in a strict supine position.

As in the human, the initial right bundle-branch block forces varied only slightly from the normal. After 12 ± 2 msec., however, the block vectors suddenly turned to nearly opposite the initial ones; in left bundle-branch block, only rarely were tiny initial upward forces present.

The mean vectors were predominantly directed superiorly (cephalad) in right bundle-branch block and inferiorly (caudad) in left bundle-branch block. Both had configurations of narrow isoscelean triangles with apices at the isoelectric point, a contour resembling that of human left, but not right, bundle-branch block. In the frontal plane, left bundle-branch block (clockwise) took a +78-degree direction and right bundle-branch block (clockwise) a −110-degree direction. In the horizontal plane, the lefts (counterclockwise) were −76 degrees and the rights (clockwise) +113 degrees. Furthermore, the normal mean mid-QRS vector was also 78 degrees in the frontal plane, identical to that of left bundle-branch block.

The recorded block forces ranged 19½ to 35 degrees from being completely perpendicular to the anatomic septum; hence, it is probable that the uncorrected tetrahedral *image* vectors, especially the left arm configurations, distorted true *cardiac* vectors in a manner similar to that seen in the human.

Occurrence and Distribution of Desmosterol in Human Arteries Following Treatment with Triparanol (P)

David H. Blankenhorn, Robert F. Maronde, and Jud R. Scholtz, Los Angeles, California

Agents which alter blood cholesterol levels by inhibition of sterol synthesis may also cause accumulation of the blocked precursor substance. Triparanol blocks conversion of desmosterol (24 dehydrocholesterol) to cholesterol. Measurable amounts of desmosterol do not occur in man unless triparanol is given, whereupon desmosterol promptly appears in blood. Therapeutic use of triparanol makes it important to know whether desmosterol accumulates in human blood vessels.

A 16-year-old boy with familial hypercholesterolemia and congenital aortic atresia was treated with triparanol, 250 mg. per day. Seventy-eight days later, despite anticoagulants, he died suddenly of coronary thrombosis. During triparanol therapy, total serum sterols varied from 400 to 500 mg. per cent, and desmosterol averaged 30 per cent of total sterol. On the day preceding death, desmosterol was 32 per cent of total serum sterol.

Vessel and liver sterols were studied by gas liquid chromatography (GLC), utilizing neopentyl glycol adipate. Twenty-seven per cent of total liver sterol was desmosterol. Atheromas from aorta, carotid, and iliac arteries demonstrated no desmosterol. However, in normal vessel wall taken between plaques, 16 per cent of total sterol was desmosterol in the aorta, 8 per cent in iliac artery.

These findings indicate that triparanol causes prompt accumulation of desmosterol in normal blood vessel walls where the composition of sterols approaches that of blood and liver. If desmosterol accumulates in atheromas, this occurs more slowly.

Dynamic Absorption Curves of Living Microscopic Blood Vessels (P)

Edward H. Bloch and Charles N. Loeser, Cleveland, Ohio

This preliminary report describes the method used and results of a study of dynamic chemical changes in the living microvascular system in situ.

The mesenteries of anesthetized frogs and rats were suspended by suturing a loop of intestine to the frame of a quartz plate and mounting the preparation on the stage of a microscope. A vessel was selected and transilluminated at a wavelength obtained by a monochromator. The image was projected onto a camera of an image orthicon or vidicon television system. Differences in optical density became differences in voltages as variations of gray in the 525 lines of the electronic image of the monitor. The differences in voltage were analyzed by selecting 1 of the lines which comprised the desired segment of the image and displaying these voltages on an oscilloscope as vertical deflections. These deflections and image were photographed at 24 f.p.s. on motion picture film. Then a test substance was injected into the gross vascular system and the substance traced from the microscopic blood vessel through vessel wall into tissue at a wavelength specific for the absorption characteristics of that substance.

Absorption spectra were obtained on the following: (1) blood in normal arterioles, capillaries, and venules; (2) mesenteric tissue at 265, 280, 350, 414, 435, 510, 570, and 625 μ; (3) T 1824 traced from the bloodstream into tissue (it passed through the walls of capillaries, not through arteriolar or venous walls); and (4) hemoglobin in erythrocytes being affected by hemolytic sera (no change in absorption).

Association of Left Ventricular Myopathy with Minor Congenital Defects of the Ventricular Septum

Daniel K. Bloomfield, Cleveland, Ohio*

Previous evidence has led us to believe that patients with smaller ventricular septal defects have a favorable prognosis, unless threatened by bacterial endocarditis. The author has collected 9 cases of minor defects of the ventricular septum in 3 living and 6 necropsied patients in whom there was some evidence of a left ventricular myopathic change, as evidenced by 1 or more of the following features: (1) early left ventricular failure, (2) S-T depression and T-wave abnormalities in the left precordial leads of the electrocardiogram, and (3) otherwise unexplained left ventricular hypertrophy at necropsy. Three of the 9 cases had small left-to-right shunts. In 6 cases, the septal defect was imperforate. Five of these 6 seen at necropsy were imperforate, either because the septal cusp of the tricuspid valve had closed the defect or because a fibrous patch presented at the site of a presumed defect. In no case was death due to the myopathy and subsequent cardiac failure. It is postulated that in some cases with a defect of the ventricular septum, the dynamics of systolic contraction are altered so as to produce a mild strain on the entire left ventricle.

Size of Ventricular Septal Defect and Its Relationship to Pulmonary Hypertension and Prognosis

Daniel K. Bloomfield, Cleveland, Ohio*

The ultimate prognosis of persons with smaller ventricular septal defects (VSD) is assumed to be favorable, but proof is lacking. The problem was approached by reviewing a major series from the literature which noted VSD size, age, and/or cause of death. To standardize defect sizes, it was assumed that an uncomplicated VSD enlarges with age in proportion to linear growth of the heart. The pulmonary valve circumference was selected as a standard for comparison. Among 115 cases reviewed, there was not 1 defect with an age-standardized size of 10 mm. or less where the cause of death was related to pulmonary hypertensive complications of VSD. In addition, 67,000 necropsies were searched for cases of simple VSD in patients dying past age 20. Twenty-five cases were found. Among these, only 5 died of pulmonary hypertensive complications, and of these, the smallest defect was 18 mm. Twelve cases showed complete or partial spontaneous closure of their defect. Of the 8 remaining, defect sizes were 3 to 12 mm. Death was due to bacterial endocarditis in 3, aortic insufficiency in 2, cor pulmonale in 1, and noncardiac causes in 2. This work confirms and extends several reports from other laboratories emphasizing the stability of VSD, as evidenced by repeated catheterizations, and it is concluded that patients having a VSD with an age-standardized size of 10 mm. or less, i.e., with a pulmonary flow less than 2½ times systemic, rarely, if ever, develop pulmonary hypertension from their defect per se.

Spontaneous Closure of Ventricular Septal Defect: Clinical and Pathologic Correlations

Daniel K. Bloomfield, Cleveland, Ohio*

Interest in spontaneous closure of ventricular septal defect (VSD) has been quickened by several recent reports. Follow-up of 24 patients with probable VSD seen between 1935 and 1939 has revealed 14 with normal hearts in 1960. Of these, among 13 with a thrill, 6 were normal. Ten of 14 cases who were tentatively diagnosed "maladie de Roger" were normal. Among 8 cases which had clinical signs of moderate shunt, 4 were normal, and 2 were improved. Review of 67,000 necropsies from 4 hospitals revealed 18 cases where spontaneous closure, complete or incomplete, was possible or probable. Three additional cases were referred to the author. From these 21 necropsies, 3 anatomic varieties of spontaneous closure were observed: (1) binding of septal leaflet of tricuspid valve, 10 cases; (2) fibrous patch formation over defect, 9 cases; and (3) tissue reaction on a presumed infective basis, 2 cases. A fourth mode, postnatal closure of the membraneous septum, of course would be missed at routine necropsy, since this would essentially be a fibrous patch within a fibrous area. In 1 instance, clinical history of a disappearing murmur correlated with the necropsy finding of a fibrous patch in the muscular ventricular septum. It is concluded that spontaneous closure of VSD occurs and probably with greater frequency than was previously thought possible.

Congenital Malformations of the Heart in Early Infancy (P)

Sidney Blumenthal, Dorothy H. Andersen, A. Gregory Jameson, and James R. Malm, New York, New York

More patients succumb to the effects of congenital malformations of the heart during the first year of life than at any comparable period. A reduction in this aspect of the infant mortality rate presupposes an appreciation of the magnitude and nature of the problem.

The findings in 426 autopsies, in which major congenital cardiac malformations were present, have been analyzed. Infants less than 1 year of age accounted for 75 per cent (320) of the total. The hypoplastic left heart syndrome, a common cause of death in the first month, was infre-

quently noted later in infancy. Anomalies resulting in marked increase in pulmonary blood flow, although a frequent cause of death in the first month, increased in frequency still further in the 1- to 6-month period. A high proportion of anomalies encountered were considered to be amenable to palliative or corrective surgery.

Eighty-four infants investigated in the diagnostic laboratory and those operated on were similarly reviewed to evaluate the nature of the clinical problem. The results of this analysis support the conclusions derived from the postmortem data.

An increasing number of critically ill infants with congential heart disease can be salvaged. Accurate diagnosis, a prerequisite to surgical intervention, requires the utilization of complicated diagnostic procedures in this age group. In many circumstances, unremitting congestive failure is present, necessitating an aggressive approach to diagnosis and treatment. Personnel in the diagnostic laboratory, as well as the surgical team, need to be oriented to the concept of cardiovascular surgical emergencies in infancy.

Protective Effect of Hypothermia in Experimental Cerebral Ischemia (P)

Robert J. Boyd and John E. Connolly, Palo Alto, California

Experiments have been performed in an effort to determine the length of time that the brain will tolerate anoxia during cardiac arrest and also to ascertain the protective effect of hypothermia in cerebral anoxia. It has been generally accepted that the human brain will tolerate 4 to 5 minutes of ischemic anoxia at normal temperatures and possibly 2 to 3 times that period at the accepted safe levels of hypothermia, 29 to 31 C. The tolerated period of cerebral anoxia at normothermic and hypothermic brain temperatures has not been experimentally established, however.

Technics have been developed in this laboratory which permit investigation of prolonged periods of cerebral anoxia at very low brain temperatures. Selective cerebral hypothermia is performed in the dog by cannulation of both carotid arteries and 1 femoral artery. Arterial blood from 1 femoral artery is cooled and pumped back into the animal through both carotid arteries. This lowers the brain temperature rapidly, while the remainder of the body stays at or near normothermic levels. In this way, any desired brain temperature can be obtained without damage to the brain from the procedure itself. Also, there is no risk of the cardiac complications which accompany general body hypothermia if it is carried below 27 to 28 C.

Cerebral ischemia was produced after the technic of Kabat and consisted of a preliminary C-2 cervical laminectomy with ligation of both vertebral arteries. One to 2 weeks later, a cervical pressure cuff was applied which effectively produced sudden, total, easily reversible cerebral ischemia with no damage to the animal from the technic itself.

Animals have been studied with the cuff technic at normal temperatures and have been found to tolerate only 8 minutes of total cerebral ischemia. At brain temperatures of 30 C., the dog will tolerate 25 minutes of cerebral ischemia. With selective cooling of the brain to 20 C., complete cerebral anoxia is tolerated for at least 1 hour.

The gross and microscopic pathology of the brains undergoing cooling and microscopic criteria of anoxic cerebral damage were also studied.

Electrocardiographic Survey on a Total, Natural Community—Tecumseh, Michigan

Ralph L. Brandt and Frederick H. Epstein, Ann Arbor, Michigan

During epidemiologic studies in Tecumseh, Michigan, including 90 per cent of all inhabitants, 12-lead electrocardiograms were taken on 2,451 men and 2,686 women age 16 and over. One or more significant abnormalities presented in 283 men and 241 women below age 50 and in 170 men and 223 women age 50 and over. Among these, Q-waves changes compatible with coronary heart disease occurred in 38 men and 10 women, major T and S-T segment abnormalities in 51 men and 50 women, various heart blocks in 45 men and 48 women, complete left and right bundle-branch block, respectively, in 6 men and 11 women and 6 men and 4 women, and atrial fibrillation or flutter in 12 men and 15 women. Left and right ventricular preponderance patterns, respectively, were seen in 149 men and 61 women and 2 men and 5 women. A history of myocardial infarction and/or angina pectoris was accompanied by major electrocardiographic changes in 25 of 65 men and 6 of 36 women. Amplitudes of R and S waves were related to age, sex, and build. R waves reflecting left ventricular activity were taller in younger men than women; this sex difference diminished with age. Similarly, with increasing age, the electrical axis shifted to the left to a greater extent in women than men. T-wave changes and S-T segment depressions were more common in women. The data provide a comprehensive account of electrocardiographic findings in a general population and reveal an unexpectedly high frequency of altered patterns among women.

Ruptured Papillary Muscle Following Myocardial Infarction with Long Survival

Gerald M. Breneman and Ellet H. Drake, Detroit, Michigan

Rupture of a papillary muscle is a rare and invariably fatal complication of acute myocardial infarction. The antemortem diagnosis has seldom been reported. Two instances of this complication were observed in a period of less than 2 years, both proved by postmortem examination. The history, physical findings, and clinical course were quite similar. Both patients sustained a posterior myocardial infarction. The appearance of the apical holosystolic murmur of mitral incompetency and severe, progressive congestive heart failure led to a correct clinical diagnosis in both cases. Long periods of hospitalization and vigorous treatment of the stubborn and eventually refractive congestive failure, including the use of corticosteroids and spirolactones in 1 case, resulted in survivals of 14 and 11 months, respectively. These are believed to be the longest reported periods of survival following this complication. Rupture of the posterior papillary muscle resulting in mitral incompetency was confirmed at autopsy in both cases.

The clinical diagnosis of this complication of myocardial infarction should be made more frequently in the future. The abrupt onset after myocardial infarction of a gross, rough, holosystolic murmur should suggest the possibility of ruptured papillary muscle or perforation of the interventricular septum. Character, location, and reference of the murmur plus findings on catheterization should help in making the proper antemortem diagnosis. Attempts at surgical repair of the condition by open-heart methods should be considered.

Attempt at Localization of the Renal Site of Action of a Mercurial Diuretic by Means of a Modified Stop Flow Technic

E. H. Bresler and J. F. Monroe, New Orleans, Louisiana

The renal site of action of mercurial diuretics has been placed by various workers at either the proximal or distal tubule. Since the earliest toxic effects appear in the proximal tubule, this has been assumed by some to represent the site of pharmacologic activity. Stop flow analysis, using mannitol to induce the high rates of urine flow required by this technic, have been interpreted as indicating a proximal site of action. Using hypertonic sodium chloride infusions in place of mannitol, we have obtained stop flow patterns in dogs before and after I.V. Mercuhydrin which suggest a distal rather than proximal site of action.

Histopathologic and Hemodynamic Reaction of the Pulmonary Vasculature to Homologous Dog Lung Antisera

Howard L. Bresler,† Richard H. Evans, Eleanor M. Humphreys, Robert W. Harrison, and Peter V. Moulder, Chicago, Illinois

Autoimmune phenomena have been extensively investigated in many organ sites, such as thyroid, kidney, and colon. The histopathologic and hemodynamic effects of intravenously administered homologous dog lung antisera have been used to study these reactions on the pulmonary vascular system. Homologous dog lung antisera were prepared by injecting lypholized, pulverized homologous dog lung into rabbits over a 3-week period, with utilization of a multiple injection site technic. Systemic and pulmonary artery pressures were recorded and cardiac outputs determined in 8 mongrel dogs. Antiserum was then administered intravenously in doses of 0.45 to 0.9 ml./Kg. body weight on 2 successive days. Within 2 days, all animals developed proteinuria. Microscopic examination of the urine revealed hyaline and granular casts, erythrocytes, and leukocytes. The proteinuria was an indication of antisera activity.

Four dogs were recatheterized 1 month later, and multiple lung and kidney biopsies were obtained. Histologic examination of the lungs revealed changes not unlike those found in pulmonary hypertension, i.e., focal endothelial proliferation of pulmonary artery interna, increase in basophilic interstitial substance (on H & E. stain), and reduction in vascularity of alveolar "spurs." The histopathologic picture of the kidney was that of a glomerulitis with increased cellularity of glomeruli, synechiae, thickening of basement membrane, and aspirated protein within tubules. None showed significant elevation of the main pulmonary artery pressure or alteration of cardiac output; therefore, calculated pulmonary vascular resistance remained normal.

Alpha-Methyl Dopa in the Treatment of Hypertension

Albert N. Brest, Gaddo Onesti, and John H. Moyer, Philadelphia, Pennsylvania

Alpha-methyl-3,4-dihydroxy-D,L-phenylalanine (alpha-methyl dopa), a decarboxylase inhibitor, inhibits catecholamine formation both in vivo and in vitro. It is logical, therefore, that this agent should possess antihypertensive effectiveness. However, although the potential hypotensive abilities

of alpha-methyl dopa have been confirmed, its mechanism remains uncertain.

The racemic mixture was administered intravenously to 15 hypertensive subjects in dosages varying from 100 to 3,000 mg. Ten of the 15 obtained significant blood pressure reductions. The hypotensive response usually began within 2 to 4 hours but was sometimes delayed for 12 or more hours. The only untoward effect was drowsiness.

The oral drug was administered to 28 hypertensive patients in dosages up to 2 Gm. per day. Of 16 patients treated with the racemate, 5 obtained significant orthostatic blood pressure reduction. Five of 12 patients treated with the levo isomer had a significant orthostatic antihypertensive response. The incidence of side-effects was low. No toxic reactions were encountered.

Acute renal and cardiac hemodynamic responses were studied in 3 patients. The antihypertensive effects were accompanied by decreased cardiac output, renal blood flow, and glomerular filtration.

Thrombelastographic Measure of the Coagulation Defects Induced by Coumarin-Type Drugs (P)

Spencer S. Brewer, Jr., Atlanta, Georgia

Specific assays show that prothrombin levels bear no relation to the reduction of proconvertin, Stuart-Prower factor, or plasma thromboplastin component in patients on any given dose of a coumarin-like drug. Nevertheless, the 1-stage "prothrombin time" is considered to be an adequate estimation of the degree of effective anticoagulation and remains the measure for laboratory control in widest use. These drugs lower the adhesive index and prolong platelet clumping, and if the 1-stage test is to reflect the behavior of the altered clotting mechanism as a whole, it must bear some direct relation to the summary effect of all those changes. Thromoelastography provides more information on fibrin formation than any other method and was thus selected to measure this summary effect. The routine laboratory prothrombin time was contrasted with thrombelastographic determinations and compared with the Owren thrombotest assay in 100 patients on long-term anticoagulant therapy. The resulting data show that some patients who are supposedly held in good anticoagulation range are under an inadequate degree of protection, while others are overdosed. The contributions made by platelets seem to be the most important items side-stepped by the 1-stage test. Any statistical evaluation of what happens to patients on or off anticoagulant therapy requires a much more critical definition of what induced coagulation defects are expected to be measured in vitro.

Hemodynamic Studies After Total Correction of Tetralogy of Fallot

J. David Bristow, George A. Porter, Victor D. Menashe, Herbert E. Griswold, and Albert Starr, Portland, Oregon

Right-heart catheterization was performed in 19 patients, 5 to 23 months after corrective surgery for tetralogy of Fallot. The ages of the patients were from 4 to 19 years. A prosthesis was used to widen the right ventricular outflow tract in all cases.

The pulmonary artery was catheterized in 17 patients. Three had no systolic gradient across the pulmonic valve. Ten had gradients below 16 mm. Hg, and the remaining 4 ranged from 21 to 34 mm. Hg. Twelve had equal pulmonary arterial and right ventricular diastolic pressures, indicating pulmonic regurgitation. Increased right atrial pressure was found in 5 of these, but it was not associated with peripheral evidence of heart failure at the time of catheterization.

The cardiac output was normal in the 13 patients in whom this determination was possible. Arteriovenous oxygen differences were less than 5.1 ml./100 ml. blood in 14 instances and 5.5 to 6.9 ml. in the remaining 5. Arterial oxygen saturation was normal at rest and/or exercise in 16 patients. Values below 94 per cent were found in 3 patients, 1 of whom had a transatrial right-to-left shunt. Unequivocal evidence of a persistently open ventricular septal defect was found twice.

The hemodynamic improvement following surgical correction correlates well with the marked clinical improvement observed in these patients. Thirteen have had an excellent result, 3 are classified as good, and 3 as fair. Small residual pulmonic valve gradients and pulmonic regurgitation are well tolerated by the majority of these patients.

Cardiodynamics in Complete Heart Block

Stanley K. Brockman, Nashville, Tennessee

Dogs having a complete heart block were used 2 weeks to 6 months after surgical division of the bundle of His. Cardiac output (electromagnetic probe) and myocardial fiber length (lever) were registered simultaneously with the electrocardiogram and left atrial, left ventricular, and aortic pressures. During the long diastole, each atrial systole caused a similar increase in ventricular pressure. Atrial pressure then declined more rapidly than ventricular pressure with a reversal of A-V pressure and closure of the A-V valve. The A-V valve then opened with decreasing ventricular and increasing atrial pressure, and the process was repeated. Thus, each atrial systole

resulted in closure of the A-V valve and a forward-and-backward flow of blood between atrium and ventricle. Each atrial systole also caused a corresponding rise in dynamic flow and pressure during the long diastole. The maximal contribution of atrial systole to initial ventricular pressure and fiber length, and thus stroke volume, was at a P-Q interval of 0.1 second.

Stepwise infusions of blood were given to construct curves relating left ventricular end-diastolic pressure to stroke work and initial ventricular fiber length. There was a descending limb to this curve at much lower end-diastolic pressures in animals having a complete heart block longer than 6 weeks. There was no descending limb in some animals having their block less than 6 weeks, even with end-diastolic pressures of 40 cm. of water. This may indicate a greater tendency to failure, the longer the block is present.

Myocardial Contractility in Extrasystoles (P)

Baruch Bromberger-Barnea, Denver, Colorado

The reduced intraventricular pressures of premature ventricular contractions and the increased pressures following a compensatory pause have, in the past, been related to changes in filling time. However, recent work on in vitro cardiac muscle sections has indicated that myocardial contractility itself changes after the introduction of stimuli. Siebens, Hoffman et al. have shown for the right ventricle and Lendrum, Feinberg, Boyd, and Katz for the left ventricle that the state of ventricular filling affects the pressure response following extrasystoles only to a minor degree.

Right and left ventricular contractility was measured in isolated, spontaneously beating dog hearts and in intact open-chest dogs as a function of the cardiac cycle. Stimuli were introduced at all parts of the cardiac cycle, and the resultant myocardial strain and/or pressures were measured. Effects of filling were eliminated by keeping both ventricular chambers empty through large openings that were cut into both chambers. Under these circumstances, the contractile force of the stimulus beat was decreased proportionally to its prematurity, while the contractile force of the stimulus + 1 beat was increased proportionally to its prematurity. This work confirms and extends the observations of previous investigators that the pressure changes observed in premature ventricular contractions are inherent properties of the myocardium and are not primarily produced by changes in ventricular filling time.

Variation in Intra-Arterial Blood Pressure (P)

Philip Brostoff, Alan Bress, and Morton Goldstein, Pittsburgh, Pennsylvania

The variation of intra-arterial blood pressure was determined in 10 normal healthy college males. History, physical examination, blood count, urinalysis, electrocardiogram, and psychologic testing were performed prior to the experiment. A polyethylene catheter was inserted into the femoral artery in the recumbent patient, and blood pressure was recorded for at least 30 seconds every 10 to 15 minutes by means of a strain gauge manometer. Each experiment lasted from 14½ to 24 hours with a mean duration of 18 hours. Pulse rate and respiratory variation and activity were recorded each time a tracing was obtained. The patient's pressure was recorded by turning a stopcock so that he could not feel anything at the time of recording.

There was a variation of systolic pressure ranging from 5 to 45 mm. Hg during any 30-second testing period and a variation of diastolic pressure ranging from zero to 35 mm. Hg. The largest variations usually occurred during sleep or restlessness. The smallest variation of systolic pressure in any patient during the entire testing period was 40 mm. Hg, and the largest variation was 85 mm. Hg. The smallest variation of diastolic pressure in any 1 patient during the entire testing period was 45 mm. Hg, and the largest variation was 60 mm. Hg.

We believe these results show the variation in arterial blood pressure in healthy young adults under the conditions of the experiment. This information may be helpful as a baseline when interpreting the effect of medicine on blood pressure.

Effect of Dextro 3:5:3′ Triiodothyronine on Serum Lipid Levels in Patients with Ischemic Heart Disease

David F. Brown, Albany, New York

The frequent association of elevated phospholipid and triglyceride levels with ischemic heart disease suggests that therapy should include means of correcting these abnormalities in addition to the more commonly recognized hypercholesterolemia. A drug possessing these properties is d 3:5:3′ triiodothyronine, which was used in a double-blind study of 23 men with ischemic heart disease, age 47 to 69 years. After 12 weeks, no significant changes in serum lipid levels had occurred in the placebo group. In 11 men who received the drug (1.0 mg. daily achieved by 0.2-mg. increments every 2 weeks), cholesterol fell from 326±34 to 268±28 mg. per cent, phospholipid from 321±51 to 271±27 mg. per cent, and triglyceride from 11.8±5.7 to 8.4±2.6 mEq./L. After 20 weeks of therapy, cholesterol levels appeared to be increasing, and an attempt was made to increase the daily dosage from 1.0 to 2.0 mg. daily in all

patients. This was achieved in the majority, but in 4 patients, angina pectoris was more frequent and severe with a dosage between 1.0 to 1.5 mg. This symptom also necessitated reduction of a 2.0-mg. dosage in an additional 3 patients. No significant increase in pulse rate and no significant weight loss were noted. At 40 weeks, the following lipid levels were observed in the original drug-treated group: cholesterol 233±45 mg. per cent, phospholipid 243±42 mg. per cent, and triglyceride 5.7±1.9 mEq./L. Lipid levels of this order were also achieved in the placebo group in whom the drug was commenced at 12 weeks.

The effective and prolonged lipid-lowering effect of this drug warrants a study of additional analogs of this type, in the hope that more complete separation of lipid lowering and calorigenic properties can be achieved.

Current Status of Anticoagulant Therapy After Myocardial Infarction

Kenneth W. G. Brown, Robert L. MacMillan, and Edward J. G. Noble, Toronto, Canada

A controlled study at the Toronto General Hospital of prolonged anticoagulant therapy in patients surviving acute myocardial infarction has failed to indicate any benefit from this treatment. Seventy-one patients were followed an average of 18 months. Thirty-seven patients received bishydroxycoumarin to maintain the 1-stage prothombin time at approximately twice normal value, and 34 patients received a placebo tablet containing 1 mg. of bishydroxycoumarin. In all other aspects, the management was identical in the 2 groups.

Nine deaths occurred in the anticoagulant patients and 3 in patients receiving placebo. Seven recurrent myocardial infarctions were observed in each group. The 2 groups were similar in aspects considered to influence prognosis.

If anticoagulant therapy offers significant benefit, one would expect a favorable trend to emerge, even in this small number of patients. The failure to demonstrate any beneficial effect caused us to examine critically the lowering of mortality reported by others.

In acute myocardial infarction, Wright et al. (1954) reported a reduction in mortality in both males and females over age 60. This has not been confirmed by a recent report from Copenhagen. In the long-term studies of Bjerkelund and the Medical Research Council, the decrease in mortality was confined to males under age 60 and to the first 6 months of treatment.

Until these inconsistencies are resolved, the exact role of anticoagulant therapy after myocardial infarction remains unsettled, but at the present time, there is little indication for continuing it beyond 6 months.

Correlative Study of the Clinical, Hemodynamic, Electrocardiographic, and Phonocardiographic Changes in Ebstein's Malformation of the Tricuspid Valve (P)

Marie J. Browne, Joan L. Caddell, Norman S. Talner, and Martin Reisman, New Haven, Connecticut

Although the auscultatory, electrocardiographic, and hemodynamic findings in patients with Ebstein's anomaly have been described previously, the mechanisms of the abnormal findings are largely unknown. By undertaking right-heart catheterization studies utilizing intracardiac electrode and phonocatheters, as well as conventional pressure recordings, oxygen studies, and external phonocardiography, we attempted to evaluate the following: (1) chamber origin of the cardiac sounds and (2) alteration in atrial, ventricular, and arterial pressure pulses brought about by the atrialization of the right ventricle.

Twelve patients in the age range 3½ to 37 years were studied. Autopsy data were available on 4 patients.

Intracardiac phonocardiography revealed a systolic ejection murmur in the small right ventricle, as well as a pansystolic murmur in the region of the anomalous tricuspid valve insertion. A loud fourth sound was recorded in the right atrium. In patients with no audible murmurs on physical examination, significant murmurs were detected by the intracardiac microphone.

Pressure tracings similar to those seen in chronic constrictive pericarditis were noted. These may suggest a hemodynamic explanation for the diminution of cardiac pulsations seen at fluoroscopy and the auscultatory finding of distant heart sounds.

A widened arteriovenous difference, suggesting diminished cardiac output, may be of prognostic significance.

Serial electrocardiograms showed progressive changes in conduction and in chamber enlargement over prolonged follow-up periods. Intracardiac electrocardiography confirmed the presence of an area of ventricular electrical activity with an atrial pressure pulse.

Atherosclerosis, Other Vascular Complications, and Lipid Pattern in Diabetic Yemenite Jews

Daniel Brunner, Tel Aviv, Jaffa, Israel

Middle-aged Yemenite Jews in Israel are known to be virtually free from ischemic heart disease, as well as other atherosclerotic processes. They have

a distinct lipid pattern, characterized by relative low total serum cholesterol level and a high percentage of cholesterol in the alpha-lipoprotein fraction. The "Yemenite lipid" is contrary to the lipid of healthy Ashkenasian Jews (of European origin).

The incidence of diabetes among Yemenite Jews is about 0.5 per cent, and this is half of the incidence of diabetes among the total Israeli population.

There are 123 diabetic Yemenites under treatment at the different public diabetic outpatient clinics.

Clinical, electrocardiographic, x-ray, and biochemical and electrophoretic examinations of 76 of them were carried out.

With the exception of 1 elderly Yemenite with a history of myocardial infarction, there were no cases of coronary artery diseases, nephropathy, or peripheral vascular diseases.

Only about 45 per cent of diabetic Yemenites retained the usual "Yemenite lipid pattern." The rest developed the lipid pattern usually found in healthy European Jews and even in coronary patients.

All recently immigrated Yemenites had the "Yemenite lipid pattern," but also 10 out of 12 patients who had suffered from diabetes for more than 10 years retained this pattern.

In regard to these results, which are in sharp contrast to the results of examinations in matched diabetics among European Jews, the question to be determined is whether the usually prescribed diabetic diet, poor in carbohydrates and rather rich in proteins and fats—and this diet is not well followed by Yemenites; their diabetic control is not so satisfactory—is responsible, at least in part, for the development of atherosclerotic and other vascular complications in diabetics.

Lipid Pattern in Yemenite Jews and in Middle-aged Coronary Patients Without Increased Total Serum Cholesterol (P)

Daniel Brunner, Tel Aviv, Jaffa, Israel

Middle-aged Yemenite Jews are well known to be free from ischemic heart disease. They are characterized by particular lipid patterns, that is, total cholesterol level under 200 mg. per cent, alpha-cholesterol in lipoprotein 28 per cent with a small standard deviation, and beta-cholesterol under 180 mg. per cent. There is no difference in the lipid pattern of young Yemenites, middle-aged Yemenites, or young European Jews (aged 18 to 20 years), but middle-aged, healthy European Ashkenasian Jews have very different lipids with a much lower alpha-cholesterol percentage (the average is about 22 per cent), very similar to the lipids in the average middle-aged American population.

Furthermore, it was found that middle-aged coronary patients are characterized by a low percentage of alpha-cholesterol (average 14 per cent ± 3.5), irrespective of their total serum cholesterol level.

In Israel, where the prevalence of ischemic heart disease is rather high, there are many middle-aged patients suffering from myocardial infarction who do not have increased total serum cholesterol. Out of 200 such cases, 50 per cent had total cholesterol level under 250 mg. per cent, 30 per cent under 220 mg. per cent, and 15 per cent under 200 mg. per cent.

Nevertheless, in the coronary patients with low total cholesterol almost similar to healthy Yemenite Jews, the alpha-cholesterol was about 14 per cent, as opposed to the Yemenites with their high alpha-cholesterol percentage. (Also, in coronary patients with total serum cholesterol about 200 mg. per cent, less than 20 per cent—and the average is 14 per cent—is in the alpha-lipoprotein fraction.)

Therefore, it appears that this particular lipid profile is more specifically characteristic of atherogenic activity than other currently used methods.

Prevalence of Coronary Artery Disease in Middle-aged Members of Collective Settlements (Kibbuzim) in Israel

Daniel Brunner, Tel Aviv, Jaffa, Israel

An investigation was undertaken on the incidence of myocardial infarction, fatal and surviving cases, among 8,500 members of Kibbuzim (communal settlements) in Israel during the last 10 years. The population group at risk was aged at the end of the 10-year survey period 40 to 60 years.

The characteristic of this epidemiologic survey was the fact that members of the Kibbuzim live in absolute equality in regard to their nutrition, housing conditions, and all other milieu factors, irrelevant of the type of work or profession. All the investigated Kibbuz members were Ashkenasian Jews of European origin. Among Kibbuz members, there were farmers, fishermen, building craftsmen, drivers, stevedores, teachers, clerks, managers, business administrators, and politicians. Therefore, it was possible to single out physical activity due to daily work as a factor in the prevalence of coronary artery disease.

Altogether, there were 111 new cases of first myocardial infarction, 34 of which died. The incidence in women was very small. The calculation with regard to annual incidence rate among men revealed that the rate in sedentary workers

was 3 times higher than the corresponding rate in nonsedentary ones (annual incidence rate per 1,000 men in sedentary Kibbuz workers 4.1; nonsedentary workers 1.36). These figures emphasize the preventive value of bodily activity against myocardial infarction in a population group which was identical in all other environmental conditions.

No evidence of a possible racial predisposition of Jewish people for coronary artery disease was found.

Comparison of mortality and incidence rates of myocardial infarction in Kibbuz members with corresponding rates among Jewish workers in the New York textile industry; with the national mortality rate from coronary artery disease in the United States, on the one hand, and in Japan, on the other hand; and with the results of epidemiologic research among London postmen revealed that the members of Kibbuzim enjoy a very low incidence rate of myocardial infarction.

Effects of an Organic Amine Buffer (THAM) in Congestive Heart Failure (P)

Charles E. Buckley, III, and Herbert O. Sieker, Durham, North Carolina

Observations in the past have suggested that acid-base balance may affect the function of the myocardium, and more recently, in animal studies, it has been suggested that the infusion of THAM increases cardiac output. Six patients with congestive heart failure and 2 individuals with compensated circulation received THAM (0.34 M solution) at rates sufficient to increase arterial pH. Cardiac output (dye method), systemic and pulterial carbon dioxide tension, increase in pulmonary arterial pressure, and systemic hypotension measured.

Four heart failure patients noted improvement in their symptoms, primarily a decrease in dyspnea and orthopnea. Significant changes were observed only when these 4 individuals developed Cheyne-Stokes respiration. Up to a 1.2 L./min. increase in cardiac output and a 10-second decrease in mean circulation time were correlated with the phases of cyclic respiration. However, there was no significant net change in cardiac output or in pressures. Two patients with cor pulmonale showed worsening of hypoxemia, elevation of arterial carbon dioxide tension, increase in pulmonary arterial pressure, and systemic hypotension during the infusion. Two individuals with compensated circulation had a slight increase in pulmonary and systemic arterial pressures with an average increase in cardiac output of 0.47 L./min. and a mean decrease in circulation time of 1.08 seconds.

These studies indicate that administration of a buffer improves the symptoms of congestive heart failure without alteration of the circulation when primary lung disease is not present. The subjective improvement noted in congestive heart failure is probably related to depression of the respiratory center which appears to be responsible for precipitating Cheyne-Stokes respiration. In patients with cor pulmonale, the infusion of a buffer may increase cardiorespiratory insufficiency.

Architecture of the Distended Vascular Wall

Donald F. M. Bunce, II, New Orleans, Louisiana

Textbook illustrations of vascular architecture classically depict the vessels in a collapsed or constricted condition. In a sense, such illustrations represent artifacts, in that they do not reflect the structure of arterial or venous walls distended with blood as they occur during life.

To compare structural differences between distended and collapsed blood vessels, segments of various arteries and veins filled with blood under normal pressure were obtained from anesthetized dogs by clamping the vessel at 2 points simultaneously, removing the section, and fixing it immediately. Corresponding sections of collapsed companion vessels, e.g., the opposite femoral artery, were obtained by conventional means. Several important differences could be distinguished histologically. For example, the lumina of distended arteries were 1.5 to 4 times larger than were their constricted counterparts, while those of distended veins were as much as 7 times larger. These findings have suggested the need for further examination of the effect of thrombi in reducing effective circulating blood volume. The constricted arterial media measured up to 4 times thicker than its width when distended. From studies of the type and volume of tissues composing the walls of arteries and veins, as well as their intramural arrangement, it appears that the structure of the wall is so designed as to resist mechanical lengthening and dilation by changes in blood pressure or other factors.

Because fundamental differences exist between the structure of the normally distended vessel and its bloodless, collapsed counterpart, investigations involving the circulation should take cognizance of the vascular architecture as it occurs within the living body.

Effects of Simultaneous Ligation of Both Common Carotid and Vertebral Arteries

Donald F. M. Bunce, II, New Orleans, Louisiana

Both common carotid and both vertebral arteries were doubly ligated and sectioned simultaneously

in 7 dogs, and some acute and chronic effects were observed. No significant changes in heart rate, temperature, or eyegrounds were noted, but marked emaciation, hair loss, and dependent edema were seen eventually in all dogs. The period of survival following operation varied between 4½ and 9 months. Since the only remaining known arterial supply to the brain is through the anterior spinal artery, it may be tentatively concluded that this vessel is capable of transporting sufficient blood to the brain to sustain life immediately following the operation. Other collateral pathways become functional later.

In a second series of 7 "control" dogs, the common carotid arteries were ligated simultaneously in 2, both vertebral and both internal carotid arteries in another 2, both vertebral arteries in another 2, and 1 vertebral and both common carotid arteries in the seventh. None of the effects which became apparent in dogs of the first group was seen in any of the "control" animals as long as a year following operation. These findings suggest that the blood flow through any 1 of the 4 major arteries supplying the head is adequate to transport sufficient blood to the brain to prevent these changes until the collateral circulation can become fully established.

Radioisotopic Renography in Evaluating Hypertensive Patients for Renal Arterial Disease (P)

Mahlon K. Burbank, James C. Hunt, W. Newlon Tauxe, and Frank T. Maher, Rochester, Minnesota

Hypertension of renal arterial origin that is potentially correctable surgically is estimated to occur in 2 to 10 per cent of hypertensive patients. The feasibility of surgical relief of renal hypertension has stimulated search for means to establish such a diagnosis clinically. Because available technics are time-consuming and not without hazard, isotopic renography has been proposed for external evaluation of function of individual kidneys in hypertensives.

Ninety-four patients with hypertension possibly of renal origin were studied by renography employing radioactive sodium iodohippurate (hippuran). Renal arteriography was done in 45 of these patients, and 22 had bilateral ureteral catheterization and specific function tests of each kidney. A continuous bruit was detected over the lateral upper abdominal quadrant in 17 patients. Ten patients had urographic evidence of unilateral atrophic pyelonephritis; 9 of these had renographic evidence of greatly diminished function of the diseased kidney. Evidence of occlusive renal arterial disease was found in 22 patients; isotopic renography revealed a significant functional difference in the 2 kidneys in 18 of these patients and less pronounced differences in 4. Seventeen patients had questionably significant alterations of renal function; 2 of them had renograms that were sufficiently abnormal to suggest renal arterial disease. Two of 45 patients with essential hypertension had abnormal renograms.

Isotopic renography is a satisfactory technic in screening hypertensive patients for evidence of renal arterial disease.

Reactive Hyperemia, Bradykinin, Digital Blood Flow, and A-V Shunts in Intact Man (P)

G. E. Burch and Nicholas DePasquale, New Orleans, Louisiana

Digital rheoplethysmographic (RPG) studies in man demonstrated digital blood flow and vascular responses to be the same for reactive hyperemia and ipsilateral intra-arterial injection of bradykinin (1 to 10 μg.). Digital responses noted for both were as follows: (1) development of flush, (2) increased warmth, (3) increased pulse volume (D_V), (4) decreased inflow (I_V), (5) lag in outflow (O_V), (6) decreased basal rate of flow, (7) increased total digital volume, (8) increased resistance to flow, (9) collecting vessels "overfilled" quickly, (10) pulse wave (D_V) reached peak slowly, (11) time between start of ipsilateral arterial pressure wave and D_V increased, (12) volume artifact decreased in magnitude, (13) little change in arterial blood pressure, and (14) no change in heart rate.

All of the findings could be explained by constriction of A-V shunts, which reduced total flow, and by dilatation of all other vessels, which increased "effective" flow to tissues. This reduces "waste" of blood through A-V "leaks" and increases "effective" flow to cells, an elegant regulatory mechanism. For the first time, the peculiar vascular response to reactive hyperemia is explained. Furthermore, the role of A-V shunts in increasing effective flow, as well as a dissimilar action (constriction of A-V shunts and dilatation of other vessels) by a single agent, is demonstrated. It is likely that local release of bradykinin as a circulatory-regulating agent occurs in response to O_2 debt.

This peculiar property of bradykinin to close A-V shunts while dilating other vessels has extreme physiologic, pharmacologic, vascular, and clinical importance. This is the first substance found which preferentially constricts A-V shunts.

Spontaneous Digital Pre- and Postcapillary Vasoconstriction and Vasodilatation and Transcapillary Filtration

G. E. Burch and Nicholas DePasquale, New Orleans, Louisiana

Spontaneous alpha and beta volume deflections are ever present in digits and other organs of man. However, their mechanism and function are unknown. To learn more about the behavior of the digital vessels during various directional phases of the alpha and beta deflections, digital rheoplethysmography (RPG) was applied to normal subjects with the right index fingertip (2RF) at heart level. It was found that whenever the alpha deflections were rising, digital inflow was increasing, and when they were declining, digital inflow was decreasing. Furthermore, when the beta deflections were rising, the collecting vessels (mainly veins) were dilating, and when the beta deflections were declining, the collecting vessels were constricting. Thus, the alpha deflections reflect a net change in caliber of the precapillary vessels and the beta deflections a net change in caliber of the postcapillary vessels.

Since alpha deflections are superimposed on beta deflections and both deflections vary independently of each other in magnitude and direction, it is evident that the digital pre- and postcapillary vessels constrict and dilate in a manner similar to that described for the pre- and postglomerular arterioles which facilitate transcapillary and glomerular filtration. This same vascular function apparently exists in the tissues in order to utilize more effectively energy from the heart to aid transcapillary filtration and lymph and interstitial and intracellular fluid flow. Aspects of functional and dysfunctional behavior of these alpha and beta deflections in normal and diseased peripheral vascular states, including congestive heart failure, have been studied.

Localization of Metabolic Lesions of Coronary Heart Disease

Lee D. Cady, Jr., Menard M. Gertler, Max A. Woodbury, and Leo J. Tick, New York, New York

Linear regressions are being used to determine localized metabolic "lesions" resembling those found associated with coronary artery disease. Individuals with these lesions are now developing overt heart disease in a proportion substantiating the validity of the method. Combined information on cardiographic patterns, blood pressure, serum lipids, family history, body build, activity, and psychometric evaluation is being used to select high-risk subjects from a stable, actively employed population of about 900 persons.

During the year 1960, 4 myocardial infarctions subsequently developed in 6 men judged to be of highest risk in this population. Results during 1961 can further substantiate the hypothesis that the metabolic causes of coronary heart disease can be associated with such factors as blood lipids, blood pressure, family history of cardiovascular disease, body build, psychologic traits, and probably other factors as well. These results are of help in the design of clinical trials of preventive measures to delay and forestall the development of coronary disease. Accurate individual estimation of proneness to coronary disease can make preventive therapy highly selective and realistic.

Graded Activity Program

Harvey D. Cain, Wallace G. Frasher, and Robert Stivelman, Los Angeles, California

The graded activity program provides a safe schedule of progressive supervised self-care activities for managing patients convalescing from recent myocardial infarction. Program performance of 335 patients has been analyzed.

Patients are started on the program not earlier than 15 days after the acute attack. The program is comprised of 10 standardized activity levels of self-care (e.g., activity level 5: dressing and level walking for 200 feet; activity level 10: tub bath and climbing 1 flight of stairs). No more than 1 level is tested per day.

Electrocardiographic monitoring is routine both prior to and immediately after performing activity levels 1, 4, 7 and 10. An activity level is repeated with electrocardiographic monitoring in the presence of (1) pulse irregularity or rise of 20 beats per minute, (2) angina, dyspnea, or fatigue, or (3) significant S-T segment shift (1.0 mm. or more). These abnormalities may indicate the necessity of delaying progress for 1 week. Total program performance is judged as (1) pass, (2) delay-pass, or (3) fail.

Electrocardiographic monitoring of early activity provides a more reliable guide to the presence of coronary insufficiency than do physical signs or symptoms. Fatigue or dyspnea were present in only 14 per cent and angina in 12 per cent of cases with electrocardiographic evidence of coronary insufficiency (23 of 166 and 20 of 166 cases, respectively). No deaths occurred within 20 hours of testing.

A patient's program performance gives a sound basis for prescribing activity in the postinfarction period; accumulating evidence indicates that a more accurate prognosis may thus be achieved.

Tone of the Small Veins in Hypertension

Francis S. Caliva, Robert M. Stafford, and Richard H. Lyons, Syracuse, New York

Normotensive and hypertensive patients of various types have been studied by the technic of digital rheoplethysmography. Determinations of

brachial artery and small vein pressures were made simultaneously, and peripheral resistance was calculated in arbitrary units $\left(\frac{\text{mean blood pressure}}{\text{flow}}\right)$.

The plethysmograms were carefully analyzed for "flattening" within the first or second pulse cycle. The first derivatives of both the inflow and outflow curves were calculated and analyzed. If the plot of the first derivative of the inflow curve reached zero within the time of the first pulse cycle, the patient was considered to have evidence of increased venomotor tone in the digit (finger).

Blood flow measurements made by this technic confirm previous studies, which have shown no statistical differences in peripheral blood flows in hypertensive and normotensive patients. There were also no significant differences in venous pressure in the 2 groups. No patient with hypertension, regardless of the etiology, was found to have increased venomotor tone in the finger. It is concluded that alterations in the peripheral circulation in hypertension are restricted to increased arteriolar tone and that the small veins are not involved.

Blood Flow Through the Superior Mesenteric Artery with Antegrade and Retrograde Perfusion of the Aorta

Rudolph C. Camishion, Yoshinori Ota, and John H. Gibbon, Jr., Philadelphia, Pennsylvania

Retrograde perfusion of the aorta during extracorporeal circulation changes the angle made by the superior mesenteric artery to the direction of blood flow from obtuse to acute. This might diminish mesenteric blood flow.

The superior mesenteric artery of dogs was exposed through a midline incision. Blood pressure in the right upper and right lower extremities was monitored by a transducer. A left thoracotomy was performed and a left atrium-to-aorta shunt established through a polyethylene tube and a roller-type pump. The distal portion of this tube was bifurcated. One limb led to the aorta through the left subclavian artery and the other through the left femoral artery. Partial bypass of the left ventricle was instituted, and the aorta was cross-clamped between the brachiocephalic and left subclavian arteries. Blood was pumped at a constant rate sufficient to maintain normal blood pressure proximal and distal to the clamp on the aorta. The aorta was perfused in an antegrade and then in a retrograde direction by clamping first the limb of the shunt to the femoral artery and then the limb to the subclavian artery. The rate of blood flow through the superior mesenteric artery, measured by a square-wave electromagnetic flowmeter, was unaffected by the direction of perfusion of the aorta under the conditions described.

Serum Lipoprotein Responses to Repeated Mental Stress

Vincent P. Carroll, Jr., Lois M. Bergquist, and Ronald L. Searcy, Los Angeles, California

Serum lipid concentrations were measured in 60 males just prior to entrance into medical school, during 2 final examination weeks, and after 1 vacation period in the freshman year. Analyses of preschool blood specimens provided a unique opportunity for evaluating the impact of a medical education on serum lipid parameters on an individual as well as a group basis. Serum total, alpha, and beta lipoprotein cholesterol were estimated after filter-paper electrophoresis, while lipoproteins of density 1.063 Gm./ml. were measured by a new microimmunochemical technic.

Elevations in serum total cholesterol associated with periods of stress were confined largely to the beta lipoprotein fraction. Alpha lipoprotein cholesterol levels showed little tendency to change from preschool values. Striking increases in serum total low-density lipoproteins during episodes of stress suggest that circulating levels of these molecules are extremely sensitive to psychologic stimuli.

In many individuals, serum low-density lipoproteins, as well as total and beta lipoprotein cholesterol levels, failed to return to preschool values, even following a period of relative relaxation. This finding suggests the possibility that continued exposure to psychologic stimuli may result in progressive increases in serum lipid fractions frequently associated with atherosclerosis.

Correction of Aortic Valve Lesions Using Cardiopulmonary Bypass

Max G. Carter, George L. Wilson, and Donald S. Dock, New Haven, Connecticut

During the past 1½ years, we have used direct operation with cardiopulmonary bypass and hypothermic cardiac arrest for the correction of aortic valve lesions in 14 patients. Nine of these had acquired aortic valve stenosis, and 3 had acquired aortic insufficiency; 2 were children with congenital aortic stenosis.

The patients with acquired aortic valve disease all had severe symptoms which included multiple attacks of syncope in 5, overt failure in 5, severe angina pectoris in all, and total heart block in 1. Two of the 9 patients with acquired aortic stenosis died following operation; 6 returned to full-time activity, and 1 is recovering nicely 2 weeks after surgery. Two of the patients with aortic insufficiency are working full-time, including the patient with total heart block whose rhythm is now

normal only 2 months after surgery. One patient remains under treatment for bacterial endocarditis, the only severe complication in the entire group. Valve replacement with individual leaflets was performed in 2 of these patients. The 2 children are well and on full normal activity.

It is our present opinion that all patients with aortic valve stenosis or insufficiency who have significant symptoms or who show electrocardiographic or roentgen evidence of progressive myocardial degeneration, should be offered surgical correction. Satisfactory extracorporeal circulation, together with hypothermic arrest by direct myocardial cooling, will allow adequate surgical correction, including valve replacement when necessary, with an acceptable mortality rate.

Correction of Mitral Stenosis and Insufficiency Using Cardiopulmonary Bypass

Max G. Carter, George L. Wilson, and Donald S. Dock, New Haven, Connecticut

Our original indications for the open approach to the mitral valve were mitral regurgitations, mixed stenosis and regurgitation, left atrial thrombosis, demonstrable calcification of the mitral valve, or reoperation for "recurrent" mitral stenosis. Generally successful results with a low mortality rate, together with the increased technical facility allowed by open-heart surgery, have influenced us to use this technic for all mitral valve surgery in recent months.

The left atrium is approached through a left thoracotomy, and pump-oxygenator connections are made by cannulation of the pulmonary artery and the left subclavian artery. Excellent exposure is thereby attained, and the risk of air embolization is minimized.

Twenty-three patients have been so treated during the past 2 years. The dominant lesion was mitral regurgitation in 8, mitral stenosis in 8, and mixed stenosis and insufficiency in 7 patients. Associated abnormalities were extensive left atrial thrombosis in 5, severe mitral valve calcification in 17, and aortic insufficiency in 4; previous closed operations for mitral stenosis had been performed in 5 patients.

Three patients died in the hospital, and 1 patient died 3 months postoperatively. Of the 19 survivors, all are working full-time as breadwinners or housewives except 1 who works half-time.

These experiences lead us to conclude tentatively that open operation using cardiopulmonary bypass is the preferred surgical approach to mitral valve problems. Final opinion must await long-term observation and critical physiologic evaluation which are now in progress.

In Vivo Estimation of Arterial Distensibility in the Lower Extremities of Man (P)

Stefan A. Carter, Winnipeg, Canada

Distensibilities calculated from pulse-wave velocity are of similar magnitude to those obtained from pressure and volume measurements. By measurement of pulse-wave velocity, arterial distensibility can be studied in intact man. However, this approach has been criticized because of the error in measurement of arterial length, which is necessary for calculation of velocity.

Since distensibility is known to vary with pressure, in the present study pulse-wave velocity was measured over a range of transmural pressures. This was achieved by applying positive and negative pressures to the outside of the extremity, while the velocity was measured by means of intra-arterial needles between the groin and the foot. The range of transmural diastolic pressures was approximately 30 to 200 mm. Hg.

Plotted against transmural diastolic pressure on logarithmic scales, distensibility declined linearly with increasing pressure up to at least 70 mm. Hg. Above 100 mm. Hg, there was usually less or no further consistent change in distensibility. The slopes of the lines relating logarithms of distensibility and of transmural diastolic pressure in the pressure range up to 7 mm. Hg decreased with increasing age. Body heating, cooling, or norepinephrine had little or no effect on the slopes, suggesting that they are relatively independent of the physiologic state of the subject. Since the slope represents the rate of change and not absolute values, it is not affected by error in measurement of arterial length and provides an index of physical characteristics of arteries which may prove useful in the study of normal and abnormal states.

Renal Hemodynamics in Congenital Heart Disease

Hector M. Castillo, Bessie L. Lendrum, Peter J. Talso, Benjamin M. Gasul, and Alfredo Vizcaino, Chicago, Illinois

Alterations in specific renal functions in patients with acquired heart disease have been well documented by several workers. Data on children with congenital heart disease have been limited. In the current study, measurements of inulin and para-aminohippurate clearances and of Tm_{PAH} have been performed in a group of 11 children who had congenital cardiac defects with right ventricular systolic pressures exceeding 50 mm. Hg. Only 1 of these children had evidence of congestive failure. Values obtained for these parameters were compared with those obtained in

8 hospitalized children with normal cardiovascular systems. In the normal control children, the mean values obtained were C_{IN} 88.3 ± 11.3 ml./min./M.², C_{PAH} 299.6 ± 42.2 ml./min./M.², and Tm_{PAH} 54.8 ± 9.2 mg./min./M.². In the children with congenital heart disease, the values obtained were C_{IN} 64.9 ± 12.5 ml./min./M.², C_{PAH} 266.1 ± 91.1 ml./min./M.², and Tm_{PAH} 48.4 ± 14.6 mg./min./M.². Statistical evaluation of these data revealed that the observed difference in C_{IN} between the 2 groups was statistically significant ($P < .001$), whereas the differences in C_{PAH} and Tm_{PAH} were not significant, ($P < 0.2$) and ($P < 0.1$), respectively. This observed decrease of C_{IN} in patients with right ventricular pressure exceeding 50 mm. Hg was an unexpected finding. It was apparently unrelated to the pulmonary arterial pressure, pulmonary blood flow, and degree of arterial oxygen saturation. There did appear to be a correlation between C_{IN} and right atrial pressure ($r = -0.68$). However, right ventricular hypertension appeared to reduce C_{IN} when right atrial pressure was well within the normal range. The significance of these findings is not unknown. The possibilities of congenital vascular malformations or neurohumoral mechanisms are being investigated.

Renal Juxtaglomerular Cells, Plasma Sodium, and Adrenal Morphology in Hypertensive Persons

Guillermo A. Celoria, New York, New York, James W. Goddard, Philadelphia, Pennsylvania, and Sheldon C. Sommers, Boston, Massachusetts

Specimens of adrenal and kidney obtained surgically or at autopsy from 54 persons were analyzed for correlated alterations of plasma sodium concentrations, juxtaglomerular (JG) indices or cell counts, and the widths of the adrenal zona glomerulosa. In human autopsy material, Pitcock and Hartroft had previously reported significant relations between measurements of these 3 factors.

Thirty-two hypertensive persons in our material demonstrated statistically significant inverse relationship ($P < 0.05$) between the plasma sodium concentration and the JG index or cell count. Only the surgically obtained material showed a significant relationship with the JG cell count. Nonhypertensive cases did not demonstrate any relation between the plasma sodium and JG morphology. No correlation of either of these measurements with the appearance of the adrenal zona glomerulosa was found.

These data are interpreted to show that changes induced by pressure in the renal JG cells may secondarily affect their secretory activities and by this mechanism influence sodium balance.

Phagocytosis of Platelets: A Source of Lipids in Human Thrombi and Atherosclerotic Plaques (P)

Arthur B. Chandler and Robert A. Hand, Augusta, Georgia

Recently, in this laboratory, the conversion of pulmonary arterial thromboemboli to typical fibrofatty atherosclerotic plaques containing foam cells (lipophages) was observed in the rabbit. The lipophages were derived from monocytes that had phagocytosed and digested lipid-rich platelets within the thromboemboli. As a result of this experiment, a study was made of human thrombi in order to determine whether or not phagocytosis of platelets could be found.

Human in vitro thrombi, made by the method previously described by Chandler, were suspended in their own plasma and incubated for periods of 1 to 6 days at 34 to 37 C. The thrombi were composed of clumps of aggregated platelets surrounded by monocytes and granulocytes and bound together by strands of fibrin. Phagocytosis of platelets by monocytes within the thrombi occurred on the second day of incubation, and the transformation of such cells to lipophages containing fat occurred by the fifth day. Swollen platelets could be distinguished in the monocytes in the early stages of fatty change. However, by the sixth day, many of the phagocytized platelets had become lysed and replaced by vacuoles characteristic of foam cells.

Human in vivo thrombi in the early stages of degeneration and organization also were found to contain lipophages similar to those in atherosclerotic plaques. Phagocytosis of platelets was observed in 58 of 134 venous and arterial thrombi which were obtained at autopsy and varied in estimated age from a few hours to several weeks. In some thrombi, transitional cells containing both fat and platelets were observed.

The observation that monocytes in artificially produced and naturally occurring human thrombi phagocytose platelets and become transformed into fat-rich foam cells (lipophages) supports the idea that atherosclerotic plaques can be derived from thrombi.

Relationship of the Urinary 17-Ketosteroid Fractions to Coronary Artery Thrombosis in the Premenopausal Female (P)

Bertram J. Channick and Louis A. Soloff, Philadelphia, Pennsylvania

The premenopausal female has a lower incidence of coronary artery thrombosis than the male of similar age. There is no evidence, however, that the premenopausal female who has suffered a myocardial infarction has an increased androgen

production compared to the normal female of similar age. Previous studies indicated that many hyperandrogenic females excrete normal or near-normal levels of total neutral 17-ketosteroids but frequently have an increased excretion of the $C_{19}O_2$ 17-ketosteroid fraction.

Urinary 17-ketosteroids were hydrolyzed and separated into their component fractions by chromagraphic separation on an alumina absorption column, using the method described by Kellie and Wade.

Eight normal controls had a mean excretion of $C_{19}O_2$ 17-ketosteroids of 4.1 mg./24 hours and a mean excretion of $C_{19}O_3$ 17-ketosteroids of 3.9 mg./24 hours. Four patients with idiopathic hirsutism had a mean $C_{19}O_2$ 17-ketosteroid excretion of 9.6 mg./24 hours and a mean $C_{19}O_3$ 17-ketosteroid excretion of 4.2 mg./24 hours. Five females who had sustained an acute myocardial infarction in the past and who still had regular menses were studied by this method. None of these had diabetes, hypertension, or hypercholesteremia. The mean $C_{19}O_2$ 17-ketosteroid excretion in this group was 6.8 mg./24 hours with a range of 5.7 to 8.9 mg./24 hours. The mean $C_{19}O_3$ 17-ketosteroid excretion was 4.8 mg./24 hours with a range of 2.4 to 6.3 mg./24 hours.

These studies suggest that females who have suffered a myocardial infarction before reaching the menopause are excreting increased amounts of adrenal androgens. Continued work is in progress to confirm these findings and also to relate increased $C_{19}O_2$ 17-ketosteroids in women without clinical coronary artery disease to their serum lipid findings.

"Risk Quotient" in Selection of Atrial Septal Defects for Surgery

Don W. Chapman, Denton A. Cooley, Edward W. Dennis, and Paul K. Peterson, Houston, Texas

From our surgical mortality and morbidity figures, a "risk quotient" rate has been derived to aid in the selection of patients for repair of atrial septal defects. In the last 145 patients with congenital heart disease, predominantly over 15 years of age, 68 have had atrial septal defects: 48 with secundum type, 7 with AV communis defects, and 13 with associated anomalies. Characteristic phonocardiographic tracings, electrocardiographic tracings, catheterization findings, and roentgenographic features were studied.

A "risk quotient" was determined by using age (below 25 = 1; 25 to 35 = 2; 36 to 50 = 3; over 50 = 4); functional capacity (1 to 4); pulmonary arterial systolic pressures (less than 25 = 1; 26 to 35 = 1.5; 36 to 50 = 2.0; 51 to 75 = 2.5; 76 to 100 = 3.0; over 100 = 4.0); shunts (left-to-right less than 3:1 = 1; greater than 3:1 = 2; right-to-left shunt = 3); and a history of previous heart failure (0 to 2). When the value is 4 to 8, there is a low risk quotient, with values of 8 to 12 a moderate mortality and a moderate morbidity, and with a value of 12 to 17, a high mortality risk is present.

In 248 cases of ostium secundum subjected to surgery, 8 deaths occurred. There were no deaths in the group of 191 below the age of 25 years. There were 5 deaths recorded in 39 cases of primum and 17 deaths in 27 patients with AV communis.

This study emphasizes the need for early diagnosis and closure because of the relentless progress of the disease.

Correction of Complete Heart Block by a Self-contained and Subcutaneously Implantable Pacemaker—Clinical and Experimental Data (P)

William M. Chardack, Andrew A. Gage, Buffalo, New York, and Wilson Greatbatch, Clarence, New York

From April, 1960 to date, 19 patients with chronic, complete, and severely disabling atrioventricular block have been treated by a subcutaneously implantable and self-contained pacemaker. The device is transistorized, battery driven, and is estimated to yield a useful life of approximately 5 years.

It emits a stimulating current of 1 msec. duration at a preset and fixed rate of between 50 and 60 for adults. These values have been arrived at by experimental observations and also by clinical investigation in the first 9 patients of this group, in whom the operation had been done in 2 stages. The electrode was inserted first, and the heart was paced with an external device. After threshold stabilization, a subcutaneously implantable pacemaker was substituted.

Currently, a 1-stage operation and a completely assembled pacemaker-electrode unit are being used. In this series of 19 patients, 1 postoperative death has occurred; a second patient died 8 months following operation. Seven complications have occurred but have been successfully corrected in 5 patients. Rehabilitation has been complete in 16 out of the 17 surviving patients. Follow-up periods range from 1 to 13 months.

The complications and difficulties which were encountered during the initial phase of clinical trial have led to modifications in the design of the pacemaker and of the electrode, especially in regard to safety and reliability of operation. The chief obstacle to long-continued pacemaking has been the problem of obtaining an electrically and mechanically stable electrode. Our observations

have led to a design which, we believe, fulfills these requirements, and this new electrode has been subjected to extensive tests.

Accuracy of Measuring Changes in the Volume of Blood in the Pulmonary Circulation and Left Heart

Andre A. Charlier, Abraham Guz, and David E. L. Wilcken, San Francisco, California

We investigated the accuracy of the indicator-dilution technic in the measurement of the blood volume between the beginning of the pulmonary artery and the root of the aorta. Two dogs were prepared with modified Kolin sine-wave transducers implanted around the pulmonary artery and ascending aorta, and flow was measured simultaneously through the 2 vessels. Changes in blood volume between the 2 transducers were produced by inflation of a balloon in the inferior vena cava.

Dye-dilution curves were recorded following rapid injection of indocyanine green through a catheter at the level of the pulmonary artery transducer with sampling at the level of the aortic transducer by a catheter connected to a fast-responding Colson densitometer. These dye curves were obtained immediately before and during partial IVC occlusion when a relatively steady state had been reached. Changes in blood volume calculated from the 2 dye curves were compared with the changes calculated from the flowmeter records of blood input and output. When blood volume changed by 10 to 30 per cent (30 to 90 ml.), the 2 methods agreed within 5 per cent. We concluded that the dye technic can measure accurately small changes in the volume of blood in the pulmonary circulation and left heart.

Effect of Acetylcholine Infusion in Chronic Pulmonary Disease Patients

Bernard L. Charms, Inoue Toshihiko, and Bernard Givertz, Cleveland, Ohio

Twenty-five patients with chronic pulmonary disease were studied during infusion of acetylcholine directly into the pulmonary artery at a rate which produced no systemic effects of the drug. Most of the patients studied had diffuse obstructive emphysema without overt fibrotis, but several had granulomas or collagen diseases with severe, diffuse, fibrotic changes. Pulmonary artery and systemic pressures, arterial oxygen saturations, and cardiac outputs were measured in the steady state by Fick principle, and pulmonary resistances were calculated before and during acetylcholine infusion. Pulmonary hypertension was present in all patients before infusion, ranging from 35 to 100 mm. Hg systolic. A fall in pressure occurred in most patients. However, in contrast to the response in hypoxic normals or patients with mitral stenosis, the higher the resting pressure, the less striking the decrease. In some with markedly elevated pressures, there was no change. In such patients, vasomotor activity must be of little or no importance in the development of pulmonary hypertension, and anatomic or extravascular factors become determinants of pressure and resistance. Arterial oxygen saturations did not show any striking fall during acetylcholine infusion. Unexpectedly, those with the lowest resting saturation had no change or an actual increase during the test period. It seems likely that vasomotor activity, believed to be responsible for maintaining ventilation-perfusion balance by restricting blood flow to hypoventilated areas of lung, is minimal in patients with chronic lung disease. Anatomic restriction of pulmonary vessels in such areas must be present.

Abnormal Diuresis Following Open Cardiotomy

Manu Chatterjee, William H. Austin, and Peter W. Rand, Portland, Maine

An abnormal diuresis has been observed in 9 of 31 patients (29 per cent) following open cardiotomy using a Mark Clowes diffusion oxygenator. These patients had urine volumes of 900 to 3,400 ml./sq. M. during the first 48 hours, an amount commonly considered excessive.

Perfusion procedure was the same for all patients except for combined hypothermia in 13 of 31 patients (42 per cent). There was no significant difference in arterial and venous pressure, electroencephalogram, arterial pH, or venous blood oxygen content to account for this observation. Postoperative fluid balance, body weight, blood hematocrit, and urine specific gravity were recorded on all patients. Urine and plasma osmolarities and electrolytes were measured on some.

Twenty-two patients showed the anticipated postoperative relative oliguria, presumably mediated in part through antidiuretic hormone release. Their urine output during the first 48 hours averaged 800 ml./sq. M. with an intake of 2,000 ml./sq. M. for the comparable period. Seven patients had excessive urine outputs averaging 1,500 ml./sq. M. for the first 48 hours with intakes of 1,500 ml./sq. M. Urine specific gravities and urine and blood osmolarities suggest a solute diuresis. One patient showed a diabetes insipidus-like response with low urinary specific gravity and a 48-hour output of 3,400 ml./sq. M. One patient diuresed 2,100 ml./sq. M. in 48 hours with an intake of 1,100 ml./sq. M. Necropsy revealed marked dehydration but a distended left atrium. The acute rise in left atrial pressure suggests that this volume receptor mechanism was present.

Our data suggest that under certain circumstances, abnormal diuresis occurs at a time when antidiuretic hormone activity should be pronounced.

Transseptal Left-Heart Cineangiography in the Diagnosis of Ventricular Septal Defect

Tsung O. Cheng, Brooklyn, New York

In the diagnosis of ventricular septal defect, there still remains a degree of uncertainty in some patients, even after a multitude of such instrumental diagnostic methods as phonocardiography, cardiac catheterization employing oxygen content analysis, nitrous oxide tests, indicator dilution studies, and conventional angiocardiography. The only certain means of definitely establishing the presence or absence of a ventricular septal defect and its whereabouts is direct visualization by contrast opacification of the defect. This information is particularly important from the surgical point of view. Right-to-left shunts can usually be clearly demonstrated by venous or selective angiocardiography. However, conventional angiocardiographic technics are notoriously unsatisfactory in demonstrating a left-to-right intracardiac shunt, mainly because of the dilution problem. By means of the modified Ross transseptal needle and cineangiocardiography, rapid left atrial injections of a contrast medium offer an ideal method for demonstrating a ventricular septal defect with a left-to-right shunt. Multiple serial injections with different planes of roentgenographic projection are employed. The method is simple and safe and is especially suitable for use in small children. Equivocal data obtained by other diagnostic technics can be clarified by transseptal left-heart cineangiography.

Respiratory Heart Rate Reflex of 1,000 Normal Subjects

Manfred Clynes and Olga Clynes, Orangeburg, New York

The respiratory heart rate (RHR) reflex is a biphasic reflex change in heart rate produced by inspiratory action and lasting about 15 seconds. On an act of inspiration, the heart rate initially increases, then decreases considerably, and finally decreases again, returning approximately to its initial rate. There is, thus, a point of maximum heart rate and a point of minimum heart rate following each other, on either side of which the heart rate has a basic resting value. The initiating cause of the reflex has been shown to be stretch receptors within the thorax. The dynamics of the time course have been analyzed with equations which are believed to represent the stretch receptor characteristics and the vagus nerve-to-pacemaker dynamic characteristics. Measurements are presented from about 1,000 subjects of both sexes and different age groups showing the amplitude and time relations to be found in presumably normal subjects and their relation to age. The course of each reflex is measured by 8 coordinates, representing the times and amplitudes of the initial, maximum, minimum, and final values. For each individual, the average of 4 reflexes is taken. Statistical analysis of these data was carried out by computers relating the parameters to age, sex, and thoracic dimension. The results indicate the RHR reflex to be an accurately repeatable physiologic measure of a neurophysiologic function, with a remarkable time course stability over wide age group ranges.

Effects of Physical Training on Metabolic and Hemodynamic Responses to Prolonged Exercise

Leonard A. Cobb, Willard P. Johnson, and Robert A. Bruce, Seattle, Washington

Serial measurements of cardiac output, heart rate, oxygen consumption, and arterial levels of lactate, pyruvate, glucose, and free fatty acids (FFA) were made during prolonged, steady, strenuous exercise (3 m.p.h., 18 per cent grade) in 15 sedentary young men and in 6 athletes. Studies were continued to the point of severe fatigue in the former group (< 40 minutes) and for over an hour in athletes, who regarded this exertion as "mild." Calculated excess lactate (XL) was used as an index of oxygen debt during exertion. In 8 untrained subjects, XL steadily rose to an average of 5.46 mM/L. at the termination of exercise. In 6 athletes, XL peaked at a much lower average level of 1.37 mM/L. within 6 minutes and fell to a low plateau thereafter while exercise continued. FFA fell initially in all subjects and rose in recovery. "Rebounds" were higher in athletes; increments in FFA varied inversely with maximum XL ($r = -0.73$) and directly with duration of exercise ($r = +0.75$). Heart rate steadily increased throughout exercise and varied directly with maximum XL ($r = +0.74$). Mean stroke volume was slightly greater in athletes. Cardiac output and oxygen consumption per minute were not altered by physical training, whereas oxygen pulse was greater ($p < .003$), heart rate slower, and XL much less in physically trained young men.

Plasma Lipid Levels in Pheochromocytoma

Burt Cochran, Jr., Shannon D. Brunjes, and Varner J. Johns, Jr., Los Angeles, California

Surgically proved pheochromocytoma patients are excellent subjects in which to assess plasma

lipid reflections of prolonged high levels of catechol amines, as well as the effects of an adrenolytic agent, phentolamine, and tumor surgery. Four such subjects were followed serially with basal levels of venous true glucose, free fatty acids (FFA), total cholesterol, lipid phosphorus and total lipids, urinary catechol amines, and gas chromatographic analysis of both FFA and whole serum fatty acids. Catechol amine excretion was predominantly norepinephrine, except in 1 diabetic subject who excreted approximately one-half epinephrine.

The following conclusions seem warranted. All 4 subjects had slightly high mean preoperative total cholesterol levels with rather wide daily fluctuations, but with prolonged hospital stay only 2 subjects had basal FFA levels significantly elevated. A 300- to 600-mg. daily oral dose of phentolamine effected a significant decrease in cholesterol and FFA levels in 3 subjects. The standard 5-mg. intravenous phentolamine test dropped the circulating FFA level by one-half in 1 subject and slightly raised it in another without much effect on other lipid parameters. Surgical removal of the tumor produced still further total cholesterol reduction in all subjects with a trend toward return of more normal levels of plasma glucose and lipids. No distinctive fatty acid changes were found, but insensitive lipolytic response to catechol amines was suggested.

Hemodynamic Effects of Intravenous Guanethidine in Man

Jay N. Cohn, Thomas E. Liptak, and Edward D. Freis, Washington, D. C.

Guanethidine was infused (0.75 to 1.0 mg./Kg.) over 5 to 10 minutes in a group of 20 hypertensive and normotensive subjects. An early transient pressor phase (mean change + 17 per cent systolic and +10 per cent diastolic) was associated with an increase in cardiac output, heart rate, and estimated hepatic-portal blood flow (EHBF). This phase was followed by bradycardia and a reduction of blood pressure (mean change from control was −23 per cent for both systolic and diastolic), the peak effect occurring at 1 to 3 hours. Cardiac output (supine) decreased moderately in 4 of 5 compensated hypertensive patients (mean −11 per cent) and rose in 2 of 3 decompensated patients (mean +18 per cent). Total peripheral resistance decreased in all 8 cases (mean −23 per cent). Right heart and hepatic vein pressures also decreased. In 3 of 5 normotensive subjects, there were slight decreases in supine blood pressure and cardiac output without significant change in total peripheral resistance.

EHBF decreased during the depressor phase in 6 of 7 compensated hypertensive patients (mean −35 per cent), while EHV resistance increased in 5 and decreased in 2 (mean +22 per cent). In 2 patients with simultaneous measurements, there was a considerable decrease in the fraction of the cardiac output perfusing the hepatic bed.

The Valsalva overshoot was blocked, and digital vasoconstrictor reflexes were inhibited following the drug; however, the effects of intravenous tyramine on blood pressure, heart rate, and cardiac output were not altered for periods up to 6 hours following administration of guanethidine. These findings suggest that catecholamine depletion is not the cause of the depression of sympathetic activity seen after a single intravenous dose of guanethidine in man.

New Method of Determining Direction of the Instantaneous Mean QRS Vectors and Mean QRS Vectors in the Frontal Plane by Dividing the Vectors into Seven Simple Groups

George W. Collen, Los Angeles, California

The hexaxial reference figure manifests the axes of the 6 extremity electrocardiographic leads with their proper polarity. The complete sector, which is 30 degrees between each axis, will be referred to as sector in the following.

Any 2 electrocardiographic instantaneous vectors of 1 extremity lead (unless a vector equals zero and is perpendicular to that lead) can be compared to the same 2 instants, respectively, of the other 5 extremity leads and projected on the hexaxial figure into 1 of 7 simple groups. Mean vectors may be similarly projected.

Group:	In the hexaxial figure, both vectors under consideration are:	
0	—projected into the same sector.	All 6*
I	—projected into adjacent sectors; separated by 0 sectors.	Only 5*
II	—separated by 1 sector.	Only 4*
III	—separated by 2 sectors.	Only 3*
IV	—separated by 3 sectors.	Only 2*
V	—separated by 4 sectors.	Only 1*
VI	—projected into sectors forming vertical angles.	All 0*

*Extremity electrocardiographic leads have the same polarity for the particular instantaneous or mean vector under consideration.

After determining the above group by mere inspection of the QRS complex, multiplying the group number by 30 degrees yields the angle between the vectors within the accuracy of 1

sector. If the vector in an electrocardiographic lead is zero or perpendicular to any 1 lead, the accuracy is pinpointed.

Similarly, the angle of any 2 instantaneous vectors can be determined from inspection of the frontal plane vectorcardiographic loop. From this angle, the above group first and then the polarity of these particular instants of the QRS complex in the 6 extremity leads can also be determined.

Wide Triphasic and Quadriphasic Electrocardiographic Waves in the QRS Interval in the Frontal Plane—A Postmortem Study of Thirty-Three Cases

George W. Collen, Los Angeles, California

A frontal plane electrocardiographic-vector study of 300 cases of cardiac pathology, proved at autopsy, revealed 11 per cent with a definite electrocardiographic pattern in which the vector study of these 33 cases did not parallel the majority of other cases. Thirty cases had triphasic (3) waves, 5 quadriphasic (4) waves, and 2 had both of these waves. These 33 cases fulfilled the following electrocardiographic criteria: (1) Only 1 of the 6 extremity leads need have wide triphasic or quadriphasic waves. (2) This particular lead must have a voltage of not less than 4 mm. (3) In this same lead, 2 of the waves in the QRS interval must be not less than 0.04 second in width, and 1 must be not less than 0.03 second. (4) If the 0.03-second wave is the first wave, the QRS interval must be not less than 0.12 second; otherwise, not less than 0.11 second. (5) The width of the first wave is measured at the isoelectric line, last wave at "junction," middle wave at a parallel line halfway between. (Quadriphasic waves need have only 3 wide waves to satisfy the above criteria.)

Pathologic findings revealed that 21 cases had localized infarction of fibrosis, and of these, 20 involved the septum. Twelve had no localization, reported as focal or diffuse fibrosis. Nineteen had endocardial or subendocardial fibrosis. Twelve had papillary muscle fibrosis. Twenty-two had combined ventricular hypertrophy. Five had left ventricular hypertrophy. One had right ventricular hypertrophy. Two cases, not included in the 22 combined ventricular hypertrophy group, had combined ventricular dilatation; only 3 had neither hypertrophy nor dilatation. Fourteen had coronary occlusions. Of these, all had septal fibrosis or infarction, and 11 had endocardial or subendocardial fibrosis.

Influence of Dichloroisoproterenol on Ventricular Fibrillation During Profound Hypothermia

Harold A. Collins, Lawrence G. Schull, James L. Guest, and Fuat Turkekul, Nashville, Tennessee

The value of hypothermia for the surgical correction of certain cardiovascular and neurologic lesions is well established. One of the limiting factors in the use of hypothermia alone has been the progressive increase in incidence of ventricular fibrillation at temperatures below 28 C. Prevention of this complication would increase the usefulness of hypothermia and could obviate the necessity for thoracotomy and pump oxygenator support in certain conditions. The effectiveness of dichloroisoproterenol in preventing arrhythmias associated with norepinephrine administration in dogs anesthetized with cyclopropane suggested its possible use in prevention of arrhythmias during profound hypothermia.

In 1 group of 10 dogs, profound hypothermia to 8 to 10 C. was produced by circulation of the oxygenated blood through a heat exchanger during total cardiopulmonary bypass. Periodically, blood samples were withdrawn anerobically for determination of pH, potassium, and carbon dioxide. After complete cessation of circulation for 30 minutes at 8 to 10 C., rapid rewarming was accomplished with the pump oxygenator and heat exchanger. In a second group of 10 dogs, the same experiment was performed, except that dichloroisoproterenol (4 mg./Kg.) was administered prior to cooling and again prior to rewarming.

Ventricular fibrillation occurred in all 10 of the control dogs and in 4 of the 10 dogs receiving dichloroisoproterenol. Three of the 10 dogs receiving dichloroisoproterenol developed ventricular fibrillation during spontaneous rewarming, and fibrillation developed in the fourth prior to the onset of hypothermia. The blood concentration of potassium, carbon dioxide, and pH did not influence the incidence of ventricular fibrillation. The results seem to indicate that ventricular fibrillation which occurs during hypothermia, presumably due to the release of catechol amines, can be effectively controlled by dichloroisoproterenol.

Morbidity and Mortality During Long-term Anticoagulant Therapy

W. Ford Connell and George A. Mayer, Kingston, Ontario, Canada

The ultimate value of long-term anticoagulant therapy following myocardial infarction can be gauged only by the deaths, reinfarctions, and hemorrhagic accidents occurring during such therapy. Several recent publications have called into question the value of this form of therapy and have suggested that the prognosis with such treatment is no better than without it, or that such benefits as do accrue are manifest only in the first year after infarction.

We have studied a group of 192 survivors of acute myocardial infarction on long-term anti-

coagulant therapy for an average period of 33 months per patient. The criteria of therapeutic adequacy were based on Mayer's standard clotting time, our sole therapeutic control. Thirty-eight deaths, 10 reinfarctions, and 33 hemorrhagic accidents occurred during the period of observation. By our laboratory criteria of adequacy of anticoagulant therapy, we found that in 26 of the 38 deaths and 8 of the 10 reinfarctions, the anticoagulant therapy was "out of control." Twenty-four of 33 hemorrhagic accidents occurred when anticoagulant therapy was clearly excessive.

In the voluminous and controversial literature on long-term anticoagulant therapy, little has been said about the adequacy or otherwise of the treatment at the time of death, reinfarction, of hemorrhage. During long-term therapy, the anticoagulant level does for various reasons, many of them unavoidable, become inadequate or excessive from time to time. Using our control method, we have demonstrated that the majority of complications occur during such therapeutic lapses. Meticulously used laboratory controls are most valuable in pointing up "management failures" and in reducing their incidence. It is our belief that the incidence of complications during long-term anticoagulant therapy is in direct ratio to the adequacy of therapeutic control.

Double-Blind Study of the Effectiveness of Long-term Anticoagulant Therapy in Myocardial Infarction

Loyal L. Conrad, Gerald L. Honick, Carryl W. Wiggins, and John D. Kyriacopoulos, Oklahoma City, Oklahoma

Fifty patients without significant disease other than acute myocardial infarction were started on long-term oral anticoagulant therapy (Phenprocoumon, "Liquamar," Organon) on the twenty-eighth day after infarction. Placebo treatment and anticoagulant groups were determined by randomization at the time the patient entered the study. Each group of 25 patients has been followed an average of 11 months (May, 1961). Patients were seen every 2 weeks for regulation of drug or placebo dosage. Physical examination, chest x-rays, electrocardiographic examinations, and other laboratory studies were done quarterly. The identity of the treatment groups was not disclosed to the examining physicians.

Preliminary results of this study in a veteran male population show that the incidence of recurrent infarction and deaths due to infarction is low, there being no difference between treatment groups. The incidence of congestive heart failure and angina following infarction is slightly higher in the anticoagulated group, although more patients with angina prior to infarction are now free from this symptom in the anticoagulated group. The low incidence for all complications, including death, in both groups is presumably related to the absence of complicating diseases, such as hypertension, diabetes mellitus, and renal disease. Any apparent benefit obtained by patients participating in this study is related to continuous observation and careful follow-up of the individual patient. As yet, the effectiveness of long-term anticoagulant therapy in this group of patients with myocardial infarction has not been demonstrated.

Skin Temperature and Digital Plethysmography in Arterial Vascular Diseases (P)

Margaret C. Conrad and Harold D. Green, Winston-Salem, North Carolina

Specialized plethysmograph and skin temperature studies, undertaken to improve methods for differentiating occlusive and vasospastic diseases, revealed the following: (1) In large artery segmental occlusion, the digital flow (venous occlusion plethysmograph) may be high or low depending on the degree of occlusion, extent of collateral circulation, and the degree of associated vasospasm. Digital pulse contours (plethysmograph) show rounded, delayed peaks, and the dicrotic notch is absent with both partial and complete occlusion. The ratio of flow to pulse normally averages 136 sd. 44.4 $\frac{\text{cm.}^3/\text{min.}}{\text{cm.}^3/\text{pulse}}$. With complete occlusion, the ratio is elevated in proportion to the percentage of the digital flow supplied by collateral circulation and to the degree of peripheral vasodilation. The presence of associated vasospasm is indicated by a significant increase in the skin temperature and flow with 120 cc. of 50 per cent alcohol orally. (2) With small artery occlusive disease, flows, pulse contours, and flow-to-pulse ratios are typical of large artery occlusion but are present only in the affected digits. (3) With vasospasm, the flow-to-pulse ratio is normal; however, the pulse has a high notch and an increased ratio of area to amplitude. (4) With both vasospasm and arterial occlusive disease, the amplitude of alpha waves increases with vasodilation; the slope of the distensibility curve ($\triangle V/\triangle P$) increases with the plateau volume (i.e., the maximal volume that could be obtained with maximal occlusion pressure), and the flow is equal to 0.46 r (when

$$r = \frac{\text{skin temp.} - \text{room temp. (20 C.)}}{\text{arterial temp. (37 C.)} - \text{skin temp.}}).$$

Activators and Inhibitors of Steroid Hydroxylation by Adrenocortical Microsomes

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We have previously shown that 10 μM catecholamines and 10 μM ascorbate, respectively, accelerate and inhibit by about 50 per cent 21-hydroxylation of steroids by adrenocortical microsomes from steer adrenals. We have now studied the action of enzyme inhibitors on this reaction. Microsomes, isolated in 0.25 M sucrose solution and washed in 0.15 M KCl, were added to a 0.15 M NaCl-2 per cent bovine albumin medium containing 20 mM glycylglycine buffer pH 7.4, 0.6 mM TPN, 3.3 mM glucose-6-phosphate, 0.4 unit glucose-6-phosphate dehydrogenase, and 0.2 mM 17 OH-progesterone. Steroid formation (2 hours, 37 C. air), determined with the Silber-Porter reaction, averaged 300 μg./mg. microsomal N.

The 21-hydroxylation was accelerated by 0.1 mM cyanide (40 to 60 per cent) or diethyldithiocarbamate (50 to 150 per cent) which also prevented ascorbate inhibition. Inhibitory were 1 mM Versene (25 per cent) or azide (30 per cent), 0.1 mM$\alpha\alpha'$ dipyridyl (30 per cent), and 0.01 mM o-phenanthroline (60 per cent). Higher concentrations of the latter 2 inhibited completely.

It appears that 2 types of metal ions are operative in the microsomal system: (1) activators ($Cu^{?}$) of TPNH oxidation, directly or via ascorbate, preventing function of the coenzyme in hydroxylation and (2) activators (Fe^{2+} ?) of the steroid hydroxylation. The nature and site of action of these cations are being studied.

These studies may be pertinent in elucidating the mechanism of action of norepinephrine and epinephrine. On the basis of our studies, it appears these substances complex copper. This suggests that the mechanism of action of epinephrine and norepinephrine may be through inhibition of copper catalysts at the target sites of the body.

Mesenteric Vascular Insufficiency due to Remote Hemodynamic Crises

Eliot Corday, Herbert Gold, David Irving, and Harold Bernstein, Los Angeles, California

Experimental and clinical evidence has been accumulated to explain ischemic changes as ulcers or necrosis of the gastrointestinal tract resulting from remote extramesenteric circulatory disturbances, such as hemorrhagic and traumatic shock, arrhythmias, myocardial infarction, and cardiac decompensation. The blood flow of the mesenteric circulation was measured during the various pathologic states with the new, accurate electromagnetic flowmeter and electronic integrator-computer. The mesenteric circulation decreases markedly during shock states, cardiac arrhythmias, and congestive heart failure. The resistance of the mesenteric circulation increases considerably as a result of vasoconstriction. This results in ischemia and necrosis of the gastrointestinal tract. Findings at autopsy have been correlated with direct measurements of the mesenteric circulation in the laboratory. Mesenteric ischemia could account for the symptoms reported in patients with the above conditions. The term "mesenteric vascular insufficiency" is proposed to explain the clinical entity.

Analysis of Indicator-Dilution Curves—Disappearance Ratios

Felix M. Cortes, J. Caulie Gunnells, Jr., and William J. Jacoby, Jr., Portsmouth, Virginia

In patients undergoing cardiac catheterization, 106 quantitative dilution curves were performed by injecting cardio-green into the pulmonary artery (PA) and/or the superior vena cava (SVC). Arterial sampling was done from the brachial artery (BA). The curves were analyzed according to the methods of Korner and Shillingford and Carter and Wood.

Disappearance ratios of 45 curves obtained from patients with left-to-right shunts were correlated with the calculated pulmonary blood flow to systemic blood flow (PBF:SBF). The disappearance ratios were normal in the cases with PBF:SBF less than 1.3:1. All ratios were abnormal when the PBF:SBF was greater than 3:1. The most sensitive indicator of the left-to-right shunt appeared to be the CL/CR ratio which was abnormally elevated in 85 per cent (39) of the curves and normal only in those whose PBF:SBF was less than 1.3:1. The spread/appearance time was the least sensitive of the ratios, being abnormal only in patients with a PBF:SBF greater than 3:1 (15 per cent) (7).

Fifty-two quantitative indicator-dilution curves were performed in the following patients: normal (21), mitral stenosis (22), and atrial septal defect (left ventricular injections) (9). In all, the disappearance ratios were normal.

In 9 patients with significant mitral insufficiency, disappearance ratios were abnormal. The CL/CR ratio was the most sensitive index.

The site of the injection was of no significance in the disappearance ratios except with large left-to-right shunts. In the latter, the curve ratios performed from the SVC gave slightly higher values, as compared to those from PA injections.

Differentiation of Primary and Secondary T-Wave Changes in the Electrocardiographic Pattern of Hypertensive Heart Disease

Richard S. Cosby, Pasadena, California, Lawrence Herman, Monterey Park, California, and Mary Mayo, Pasadena, California

Controversy over the significance of the electrocardiographic patterns of left ventricular hypertrophy has centered on the interpretation of ST-T changes. The problem is whether the ST-T abnormalities are purely secondary to the increasing magnitude of the QRS vector or whether they represent an additional complication, i.e., a preliminary T-wave change. Adequate analysis of these relationships must include clinical-electrocardiographic correlations over the entire life span of developing hypertrophy. From the Los Angeles County Hospital 9 patients with hypertensive heart disease were selected whose records contained both a normal control electrocardiogram and subsequent abnormal tracings including 1 within 6 months of death. Thirteen private patients were chosen who had been followed at least 5 years and who had progressive electrocardiographic changes starting with a normal pattern. Each series of tracings showed stepwise increases in voltage QSR (recorded primarily in the horizontal plane).

The results were divisible into 3 separate and approximately equal groups. In the first, QRS changes were dominant and ST-T changes always minimal. In the second, QRS changes were accompanied by ST-T changes progressing to flattening and inversion of T. In the third group, ST-T changes were disproportionate to incremental changes in QRS. The 3 groups appear to represent (*a*) pure work hypertrophy, (*b*) work hypertrophy sufficient to produce relative coronary artery insufficiency, and (*c*) distinct coronary artery changes superimposed on the pattern of left ventricular hypertrophy.

Digital Computation of the Spatial Ventricular Gradient in Normal and Premature Ventricular Contractions and Intermittent Bundle-Branch Block

John Cosma, Friedemann W. Stallmann, and Hubert V. Pipberger, Washington, D. C.

Wilson postulated that the ventricular gradient should remain constant, regardless of changes in the pathway of activation. In the past, tests of this hypothesis have been limited mostly to the frontal plane. In 3-dimensional determinations, leads without constant lead strength were used.

In the present study, the spatial ventricular gradient ($SV\hat{G}$) was determined in 49 cases with premature ventricular contractions (PVC) and 2 cases with intermittent bundle-branch block by means of a corrected orthogonal lead system with relatively constant lead strength and direction. Records were taken on magnetic tape and subsequently digitized. Time integrals of each lead were obtained through digital computation, determining spatial magnitude and direction on the basis of the orthogonal components.

The spatial angle between $SV\hat{G}$ of normal beats and PVC ranged from 5 to 144 degrees with a mean of 51 degrees. The difference in magnitude ranged from −34 to +37 mV/msec. with a mean of +8 mV/msec. In cases where the $SV\hat{G}$ magnitude of PVC was found smaller than that of normal beats, a negative value for the difference was used. PVC of right or left ventricular origin did not differ significantly.

In 1 case with intermittent right bundle-branch block, the spatial angle between $SV\hat{G}$ of normally and abnormally conducted beats was 58 degrees and the difference in magnitude −8 mV/msec. In another case with intermittent left bundle-branch block, these differences were 70 degrees and −27.3 mV/msec. These data indicate significant changes in direction and magnitude of $SV\hat{G}$ when the pathway of activation is altered.

Role of Calcium and Lanatoside-C in Oxygen Consumption in Human Myocardial Tissue Slices (P)

Lamar Crevasse and Myron G. Wheat, Gainesville, Florida

The principal purpose of this investigation was to determine the effects on oxygen consumption of lanatoside-C and its relationship to calcium. Human cardiac tissue slices obtained from open-heart surgery were incubated in Krebs-Ringer phosphate with and without calcium; 10 mM glucose, pyruvate, and succinate were utilized as substrates. The direct method of Warburg with oxygen as the gas phase was used for determining oxygen consumption. A final concentration of 1 x 10^{-6} molar crystalline lanatoside-C was added from the sidearm after 1½ hours incubation, and changes in oxygen consumption were followed for an additional 1½ hours. In this manner, each tissue slice served as its own control. The introduction of lanatoside-C produced and maintained a striking increase in oxygen consumption independent of exogenous substrate. The presence of the calcium ion was essential for this acceleration of oxygen consumption. With calcium present in the media, the following increases in qO_2 after introduction of lanatoside-C were observed: no substrate 2.3 to 6.3, glucose 2.6 to 7.7, pyruvate 3.0 to 5.2, succinate 9.7 to 11.0. In the absence of calcium, no appreciable increase in qO_2 was observed after introduction of lanatoside-C: no substrate 2.0 to 1.8, glucose 2.8 to 2.0, pyruvate 2.7 to 2.2, succinate 8.5 to 8.2.

This study demonstrates a direct effect of lanatoside-C in markedly increasing oxygen utilization in human myocardial tissue slices independent of substrate. The acceleration of oxygen consumption after the introduction of lanatoside-C is dependent on the presence of calcium.

Maximum increases of oxygen consumption occurred in tissue respiring in Krebs-Ringer phosphate alone or with glucose as the substrate. This metabolic relationship is similar to the glycoside-calcium dependency in myocardial contractibility.

Cineangiocardiography in the Differential Diagnosis of Tetralogy of Fallot

J. Michael Criley† and Catherine A. Neill, Baltimore, Maryland

Ten patients with cyanotic congenital heart disease with pulmonic stenosis were studied by image amplifier cineangiocardiography combined with cardiac catheterization. Of these, 8 had undergone 1 or more systemic-pulmonary anastomoses. The patients, aged 5 to 26, were subjected to study in order to delineate the anatomy of their cardiac defects and to assess their eligibility for open-heart surgery.

The femoral vein or artery was catheterized percutaneously according to the Seldinger technic by means of roentgenopaque polyethylene catheters. The site of selective contrast medium injection was chosen after preliminary analysis of intracardiac pressures and oxygen saturation.

Five were found to have tetralogy of Fallot, 2 had transposition of the great vessels, 2 had functionally single ventricles, and 1 had an intact septum with a hypoplastic right ventricle. The motion picture studies were particularly valuable in illustrating the following: the size and location of ventricular defects in differentiating tetralogy from single ventricle; the relationship of the great vessels to ventricular defects in differentiating overriding from transposition; the site, severity, and physiologic variation of pulmonary outflow tract obstruction; the size and functional capacity of the right ventricle; and the dimensions of the vessels utilized in systemic-pulmonary shunts.

Cinecatheterization has proved to be of great value in the differential diagnosis of tetralogy of Fallot from more complex cardiovascular malformations which are not amenable to total surgical correction.

Mitral Valve Function in Man (P)

J. Michael Criley† and Richard S. Ross, Baltimore, Maryland

The functional anatomy of the mitral valve has been studied with image amplifier cineangiocardiography in 15 patients. Roentgenopaque polyethylene catheters were inserted percutaneously into the femoral vein and over a transseptal needle into the left atrium. Motion pictures were taken at 60 frames per second during the injection of contrast material into the left atrium.

Atrial systole, mitral valve closure, ventricular systole, and mitral valve opening have been related to the electrocardiogram, phonocardiogram, and intracardiac pressures. Mitral valve closure or the cessation of mitral valve flow can be seen to precede the onset of ventricular systole.

Characteristic alterations in the mitral valve contour occur in the presence of mitral stenosis and mitral regurgitation. The size of the mitral valve orifice can be estimated and the presence or absence of retrograde flow noted. Pulmonary venous reflux of contrast material normally occurs with atrial systole but also occurs with ventricular systole in patients with mitral regurgitation. The delayed mitral valve closure and the accelerated valve opening of mitral stenosis can be precisely timed and visually demonstrated.

Cineangiocardiography provides an excellent method for estimating chamber size and the effectiveness of contraction. Poor left ventricular emptying is often seen in patients with mild mitral stenosis whose symptoms are out of proportion to the degree of mitral valve obstruction.

Hemodynamic Effects of *l*-Norepinephrine and Ouabain in Dogs Following Acute Myocardial Infarction

Robert P. Cronin and Juan B. Calatayud, Montreal, Canada

Hemodynamic effects of *l*-norepinephrine (NE) infusion and of rapid digitalization with ouabain were studied separately in 10 dogs. Five dogs underwent ligature of the left anterior descending coronary artery (L.A.D.) 2 to 7 days prior to the study. The remainder underwent a similar operation but without coronary ligation. Cardiac outputs (CO) were determined by the Fick method. NE was infused at a rate of 10 to 15 μg./min. for 30 minutes. CO and mean arterial blood pressure (M.B.P.) were determined prior to, during the last few minutes of, and 30 minutes after cessation of NE infusion. Total peripheral resistance (T.P.R.) was calculated.

Prior to NE infusion, M.B.P. averaged 22 per cent lower in the L.A.D. group, but no significant difference was observed in CO. During NE infusion, M.B.P. rose an average of 26 per cent in the L.A.D. group and 20 per cent in the controls. CO rose 28 per cent in the L.A.D. group and 82

per cent in the controls. T.P.R. fell in both groups.

Two days after NE infusion, both groups were restudied; data were obtained prior to the intravenous administration of 0.5 mg. ouabain and 30 and 60 minutes later. CO decreased an average of 23 per cent in the L.A.D. group and rose 37 per cent in the controls. No significant change in M.B.P. was observed in either group.

These data emphasize the primary inotropic effect of infused NE. The modified CO response to NE in the presence of myocardial infarction cannot be explained on the basis of ventricular failure alone in view of the negative response of this group to ouabain.

Digitalization as a Treatment for Irreversible Hemorrhagic Shock

Jack W. Crowell, Jackson, Mississippi

The mean right and left atrial pressures, the mean pulmonary arterial pressure, and the mean systemic arterial pressure were measured simultaneously in 21 anesthetized dogs subjected to 30 mm. Hg systemic arterial pressure and in which the viscosity was maintained constant by control of the hematocrit ratio. Cardiac output and peripheral resistance were determined under similar conditions by use of a continuous cardiac output recorder.

During the transition from reversible shock to irreversible shock, there was no change in the peripheral resistance of the animals; however, in all cases there was a rise in either right or left atrial pressure, indicating failure of the heart.

Animals in which irreversible hemorrhagic shock was produced by placing the animals in lethal oxygen debts showed that digitalization by ouabain resulted in survival of animals that would ordinarily have died of irreversible shock. After an oxygen debt of 120 cc./Kg., only 50 per cent of the control animals lived, whereas 100 per cent of the treated animals lived; after an oxygen debt of 150 cc./Kg., all control animals died, but 80 per cent of the treated animals survived. The data suggest that irreversible shock is a cardiac phenomenon and that drugs acting on the heart are beneficial. (All percentages are based on groups of 10 dogs.)

Unusual Manifestations of the Infant Patent Ductus Arteriosus

Kenneth Cruze, Larry P. Elliott, Gerold L. Schiebler, and Myron W. Wheat, Jr., Gainesville, Florida

Isolated patent ductus arteriosus usually presents with a characteristic clinical picture. Although there are variations in symptomatology, there is usually little difficulty in making the diagnosis. Occasionally, however, this picture is so bizarre that it may be impossible to make the diagnosis without recourse to retrograde aortography and/or cardiac catheterization.

A summary of the unusual clinical findings in 6 infants emphasizes the wide and unusual spectrum of the infant ductus. These findings fell within 3 clinical areas: auscultatory, electrocardiographic, and roentgenologic.

Three patients had unusual auscultatory findings: One had only a diastolic murmur in the pulmonary area; another had only a loud systolic ejection click. A third had an apical regurgitant murmur of mitral insufficiency; this patient also had an enormously enlarged left atrium by roentgenographic and electrocardiographic criteria. A fourth infant presented with a murmur indistinguishable from a ventricular septal defect.

Another infant demonstrated on vector electrocardiography the findings usually ascribed to an endocardial cushion defect with the mean QRS being −65 degrees in the frontal plane.

The sixth infant had a systolic murmur heard best in the back with the typical blood pressures obtained in coarctation of the aorta.

These patients are presented to emphasize the many clinical facets of an infant patent ductus arteriosus.

Hemodynamic and Blood Catecholamine Patterns During a Standard Cold Pressor Test (P)

Richard P. Cuddy, Harold Smulyan, Charles R. Markason, John F. Keighley, and Robert H. Eich, Syracuse, New York

The relationship between hemodynamics and catecholamine (CA) changes during the cold pressor test was studied in 11 normals and 12 subjects with labile blood pressure. Cardiac output (COP) was determined by the indicator-dilution method and blood catecholamines by the trihydrohyindole method of Von Euler.

Of 11 measurements in 6 normal subjects, the COP fell with the cold pressor in 7 (mean −0.12 L./min.); the total peripheral resistance (TPR) rose in 9 (mean +99.7 dynes/cm.$^{-5}$/sec.); the arterial norepinephrine (NE) increased in 6 (mean +0.28 γ-/L. plasma), and arterial epinephrine (E) increased in 3 (mean +0.10 γ-/L. plasma). The CA changes were parallel in direction but not magnitude to the changes in TPR in 6 measurements and opposed in two; in 3 observations, the CA remained at 0 in spite of a rise in TPR. Likewise, there was no relationship between the magnitude of the blood pressure response and that of the CA.

In 7 observations on 5 subjects with labile blood pressure, the hemodynamic responses were variable, and in only 1 did the catecholamine change parallel TPR.

Atropinization, using 1.2 mg. I.V., did not alter the response of 4 normal subjects. However, in 8 labile hypertensives, the hemodynamic response was much more consistent, COP rising in 6 (mean + 0.86) and TRP increasing in 7 (mean + 44); in 5, the CA changes were in the same direction as the TPR changes.

These data suggest that, especially in labile hypertension, the hemodynamic responses to the cold pressor may vary and are not determined solely by catecholamine changes.

Alteration of Cardiac Shunts with Amyl Nitrate and Angiotensin—Diagnostic Implications

Gordon R. Cumming, Winnipeg, Canada

During heart catheterization in patients with congenital heart disease, systemic resistance was lowered by amyl nitrate inhalations and raised by angiotensin infusions. Pressure changes were monitored and flow changes assessed by dye-dilution curves. Amyl nitrate reduces left-to-right shunts in cases of atrial septal defect, ventricular septal defect, and patent ductus. Conversely, right-to-left shunts are considerably increased and, again, at the atrial, ventricular, and pulmonary artery levels. In balanced situations where no shunt is present, such as pulmonary stenosis with ventricular septal defect, amyl nitrate produced a right-to-left shunt and permitted the correct diagnosis. In one case of pulmonary stenosis and ventricular septal defect, an entirely left-to-right shunt was changed to a pure right-to-left shunt. Angiotensin increased left atrial, left ventricular, and aortic pressures, and changes in pulmonary pressure appeared to be passive. Left-to-right shunts increased in percentage, and shunts that were not detected under control conditions were made apparent. All types of right-to-left shunts were diminished by angiotensin, and small shunts were abolished in cases of tetralogy, Eisenmenger's syndrome, and pulmonary stenosis with patent foramen ovale.

Etiology of Atrioventricular Heart Block: A Study of Its Relevance to Prognosis and Pacemaker Therapy (P)

George W. Curd, Edward W. Dennis, Alfredo C. Montero, Paul K. Peterson, Raymond D. Pruitt, and Sidney Schnur, Houston, Texas

A series of 132 cases of complete atrioventricular heart block (CAVB) of varied etiology was reviewed to appraise the natural history of this arrhythmia and factors bearing on prognosis. Each case was studied specifically to ascertain whether artificial pacemaker therapy might have been employed to alter longevity or symptomatology favorably.

Results of this study support the following conclusions: (1) The incidence of CAVB parallels, as regards age and sex, the incidence of the associated organic heart disease to which the block is secondary. (2) The prognosis in patients with CAVB shows a more evident correlation with the severity of the underlying heart disease than with complications stemming from the block itself, i.e., Stokes-Adams seizures, bradycardia, catastrophic ventricular arrhythmias. (3) Categories of cases having a prognosis better than the average for the entire group were (*a*) congenital heart block, (*b*) CAVB developing secondary to a cardiac surgical procedure, (*c*) cases wherein the organic cardiac lesion responsible for CAVB could not be identified, and (*d*) CAVB secondary to digitalis intoxication. (4) Categories of cases having a prognosis poorer than the average for the entire group were (*a*) coronary artery disease, (*b*) valvular heart disease, (*c*) CAVB due to miscellaneous causes, and (*d*) hypertensive disease. (5) Optimal pacemaker therapy would have altered the prognosis in less than 10 per cent of the total patients studied.

A favorable influence on survival by optimal pacemaker therapy appears most likely in CAVB after cardiac surgical procedures and in CAVB in patients in whom a specific organic cardiac lesion could not be identified.

Blood Gas Changes Following Correction of Cyanosis Producing Right-to-Left Shunts

Martin L. Dalton, Jr., and James D. Hardy, Jackson, Mississippi

It has been demonstrated by several investigators that arterial CO_2 content is normal or below normal in congenital cyanotic heart disease. The explanations of this phenomenon are numerous and diverse, ranging from increased rate of flow to increased hemoglobin levels. Hyperventilation has also been suggested as a cause. The present study bears upon the problem.

Cyanosis was produced in 12 adult mongrel dogs by forming a large pulmonary arteriovenous fistula. Blood gas analysis and blood volume studies using T 1824 dye were done at monthly intervals. After 6 months, the fistula was closed with a heavy silk ligature, and the laboratory determinations were continued as before.

Typical changes were demonstrated beginning 1 month after the first procedure. These included

marked elevation of hemoglobin, hematocrit, red blood cell count, total red cell mass, and arterial CO_2. The most striking changes were encountered following closure of the fistula. Within 3 months, the arterial CO_2 had fallen from a mean of 35.98 volumes per cent to 18.04 volumes per cent in 7 surviving animals, while the arterial O_2 content rose from a mean of 15.28 to 20.08 volumes per cent. To date, the polycythemia remains unchanged, but the mean blood volume is returning to baseline levels.

The induced changes associated with a large right-to-left shunt and their reversibility have been studied. The decline of arterial CO_2 levels to subnormal levels is statistically significant. The pathway of occurrence of this phenomenon remains obscure thus far.

Observations on Sixty Patients Operated on for Aortic Insufficiency

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Sixty patients with pure or significant aortic insufficiency have been operated on at the University of Virginia Medical Center. All patients have been subjected to a left-heart catheterization and most to a combined left- and right-heart catheterization in addition to the standard clinical and laboratory studies. Many patients have been followed during the early postoperative period by means of cannulas implanted in the right and left sides of the heart, central veins, and central aorta. In these patients, data on blood gases and pulmonary function are available. A large number of patients were recatheterized several months postoperatively. Autopsy findings from those patients who failed to survive have been correlated with preoperative studies.

The following aspects have been studied: (1) influence of the primary disease process on the surgical results; (2) the relationship of electrocardiographic changes to observed heart size, hypertrophy, fibrosis, and operability; (3) changes occurring in the central aortic and brachial artery pulse wave, ventricular ejection time, and pulse pressure before and after corrective surgery; (4) the role of left ventricular chamber size in the immediate post-pump period; (5) the role of mitral insufficiency and chronic pulmonary congestion ("stiff lung") during and after surgery; (6) the marked fluctuations in vasomotor tone which occur immediately postoperatively; and (7) our present criteria for the selection of patients for surgery.

Dilatation of the Heart Following Coronary Occlusion; Role of the Pericardium in the Postocclusion Hemodynamic

Callisto A. Danese, Nicola San Martino, Philadelphia, Pennsylvania, and Anex Papaioannou, New York, New York

The dilatation of the heart which occurs after ligating a major coronary branch may exceed the capacity of the pericardium, with consequent constriction of the enlarging heart. This constriction interferes with the filling of the right heart and the postocclusion hemodynamic, although no influence on the mortality rate and, specifically, on the incidence of early ventricular fibrillation has been observed.

In 55 per cent of 26 dogs in which the circumflex was ligated and the pericardium closed and in 45 per cent of 28 dogs in which the pericardium was left open, early ventricular fibrillation occurred. In separate observations on 20 animals subjected to coronary ligation, the production of coronary tamponade one-half hour later did not initiate ventricular fibrillation. Constriction of the heart, therefore, does not seem to initiate ventricular fibrillation. In the animals which did not fibrillate, continuous observation for 1½ hours after the ligature demonstrated, in the animals with closed pericardium, an average drop of the systolic blood pressure of 20 per cent of the starting values, an average increase of the venous pressure of 5 cm. of water; the heart rate increased in half the experiments. In the animals with open pericardium, the arterial pressure fell off 15 per cent, the venous pressure did not increase, and the cardiac rate decreased in all but 1. At autopsy, marked congestion of the liver was found in the first group, whereas in the second group the congestion was more marked in the lungs.

Comparison of Electrocardiographic and Ballistocardiographic Findings with Those Obtained by Coronary Arteriography (P)

Frank W. Davis, Jr., Baltimore, Maryland

Coronary arteriograms were performed on a select group of 35 patients, who were under consideration for coronary endarterectomy or who presented chest pain about which some doubt existed after careful investigation by conventional methods. The degree of atherosclerotic involvement of the coronary arteries was estimated from these films (either biplane static films, or cinearteriograms, or both). These estimates were then correlated with (1) the resting electrocardiogram, (2) the electrocardiographic 2-step test, (3) the resting ballistocardiogram (high-frequency Starr type), (4) the ballistocardiographic cigarette test,

and (5) the total serum cholesterol level.

Six patients had normal arteriograms, 11 minimal to moderate changes, and 18 showed severe obstructive changes in 1 or both main coronary arteries.

The electrocardiogram was abnormal in half of the subjects with normal arteries, normal in the majority of those with minimal or moderate atherosclerosis, but abnormal in 60 per cent of those with severe disease. Single and/or double 2-step tests were positive (1.5 mm. S-T depression) in half of those with extensive atherosclerosis and were negative in all others. Borderline (0.5 mm. S-T depression) responses occurred in 50 per cent of those with less extensive lesions but also in 40 per cent of those with normal arteriograms.

Ballistocardiograms were abnormal in half of the atherosclerotic subjects, and the ballistocardiographic cigarette tests were "positive" in only half.

Serum cholesterol levels were markedly elevated (over 350 mg. per cent) only in patients with moderate or severe vascular lesions but were normal in the subjects with atherosclerosis as often as in those with normal arteries.

Given the limitations of small numbers (35) and youth (mean age 43), this comparison of laboratory methods in evaluating possible ischemic heart disease emphasizes the limitations of current technics. The 2-step test (using 1.5 mm. depression as positive) is least subject to "false" positive responses, but less strict criteria lead to less discriminating results.

Acute Effects of Cardiac Glycosides on Aldosterone Secretion in Dogs with Hyperaldosteronism Secondary to Chronic Right Heart Failure

James O. Davis, Charles C. J. Carpenter, Carlos R. Ayers, John E. Holman, Bethesda, Maryland, Charles R. Wallace, and William F. Hamilton, Augusta, Georgia

Experimental congestive heart failure was produced in dogs by controlled progressive pulmonic stenosis alone (6 dogs) or by a combination of tricuspid insufficiency and pulmonic stenosis (2 dogs). Naturally occurring right heart failure was studied in a dog with mitral valve disease. The concentration of aldosterone in adrenal vein plasma was measured by the double isotope derivative procedure. During control observations, aldosterone secretion was markedly elevated (0.10 μg./min. compared with a normal value of 0.024 μg./min.); mean right atrial pressure was also strikingly elevated, and sodium retention was virtually complete. Digoxin (1.2 to 1.5 mg. intravenously) given to the 6 dogs with cardiac failure secondary to pulmonic stenosis decreased right atrial pressure from 17 to 10 cm. water, increased mean arterial pressure from 110 to 126 mm. Hg, and decreased aldosterone secretion from 0.088 to 0.039 μg./min. (55 per cent). The decline in aldosterone production was evident 1 to 2 hours after digoxin injection. Ouabain (1 mg.) was administered intravenously to the dog with naturally occurring cardiac failure; marked improvement in cardiovascular function was followed by a drop in aldosterone secretion within 1½ hours from 0.084 to 0.014 μg./min. (83 per cent). In contrast, the dogs with tricuspid insufficiency and pulmonic stenosis given 1.3 mg. of digoxin intravenously failed to show a change in arterial pressure, while right atrial pressure was slightly increased, presumably due to increased tricuspid regurgitation; aldosterone secretion was essentially unchanged. The data are consistent with the view that cardiac glycosides decrease aldosterone secretion as a consequence of improvement in cardiovascular function.

Metabolic Basis for the Action of Antidiuretic Hormone

Robert P. Davis and Mitzy Canessa-Fischer, New York, New York

Antidiuretic hormone applied to the urinary bladder of the toad *(Bufo marinus)* has been shown to lead to an increase in oxygen consumption proportional to an increase in sodium transport. The mechanism of coupling of the energy derived from oxygen consumption to active ion transport is unknown for any tissue. We have identified intermediates of energy metabolism during and in the absence of measurable active ion transport by application of fluorescence spectroscopy to the *surviving, intact,* isolated toad bladder. These intermediates include free reduced pyridine nucleotide, protein-bound reduced pyridine nucleotide which is specifically coupled to oxidative phosphorylation, flavins, and tissue proteins. We have also shown that energy-rich pyridine nucleotide is a common pathway by which various substrates, such as glucose, pyruvate, and succinate, may provide energy for active ion transport. Antidiuretic hormone leads to a 4- to 6-fold enhancement of the concentration of the bound pyridine nucleotide associated with high energy phosphate formation. Adenosine diphosphate exerts "metabolic control" by effecting a striking reduction in the tissue concentration of energy-rich pyridine nucleotide and an increase in oxygen consumption by the toad bladder. The effect of antidiuretic hormone on pyridine nucleotides is similarly reduced by adenosine diphosphate. These results give information on the pattern of intermediary metabolism in the toad bladder and

suggest that the effects of antidiuretic hormone on sodium transport and oxygen consumption are mediated through effects on the interaction of energy-rich pyridine nucleotide and adenosine diphosphate in the bladder.

Controlled Study of the Effects of a Diet High in Unsaturated Fat (P)

Seymour Dayton and Morton Lee Pearce, Los Angeles, California

Middle-aged men living in a Veterans Administration domiciliary unit have been randomized, following baseline evaluations, into 2 groups. The control group receives a conventional diet of 2,400 calories with 40 per cent of the calories derived from fat. The fat has (by analysis) an iodine value of 55, polyunsaturated fatty acid content 15 per cent, and saturated fatty acid content 44 per cent. The experimental group receives a diet of similar composition, except that the fat has an iodine value of 100, polyunsaturated fatty acid content 38 per cent, and saturated fatty acid content 26 per cent. Food is served *ad libitum*.

The project is carried out on a double-blind basis. Thus far, 613 subjects have been randomized.

Acceptance of the experimental diet has been good but not complete. In both groups of subjects, 19 per cent of meals have been missed or eaten elsewhere. Withdrawals (not including discharges from the center) have numbered 45 of 310 experimental subjects, as compared with 12 of 303 controls.

The experimental diet has resulted in an average plasma cholesterol drop of 29 mg. per cent from a mean baseline value of 232. This depression has been maintained over a follow-up period of up to 16 months. Plasma total lipids of the experimental group have shown no consistent change. Plasma cholesterol of the control group has risen 15 mg. per cent, and a progressive rise from 840 to 970 mg. per cent has been observed in their total lipids. Average body weights have remained constant in both groups.

Data obtained thus far on morbidity and mortality are too few to permit conclusions.

Effect of Sympathetic Blockade on the Accelerated Cardiac Output of Hyperthyroidism (P)

William J. deGroot, Frank W. Kroetz, James J. Leonard, Galveston, Texas, Hyman W. Paley, San Francisco, California, and James V. Warren, Columbus, Ohio

The increased cardiac output of experimental hyperthyroidism has been abolished by operative epidural sympathetic blockade. This would imply that the circulatory effects of thyroid hormone are mediated entirely through the sympathetic nervous system. To evaluate this hypothesis, hemodynamic studies were performed on 3 groups of 21 hyperthyroid patients. Studies were done before and after administration of 2 peripheral sympathetic blocking agents and 1 ganglionic blocking drug. In addition, triiodothyronine was given to 1 patient with naturally occurring autonomic deficit.

Reserpine was given intramuscularly to 14 patients in doses of 7.5 to 20 mg./day for 3 to 5 days. Although the pulse slowed from 108 to 85 beats/min. ($P < 0.01$), the cardiac output was not altered (5.9 to 6.1 L./min./M.^{2}, $P > 0.5$). The second sympathetic neuroplegic, guanethidine, was administered orally to 7 patients in doses of 150 to 300 mg./day for 3 to 6 days. Heart rate decreased from 109 to 86 beats/min. ($P < 0.01$). Cardiac output was unchanged (5.7 to 5.4 L./min./M.^{2}, $P > 0.5$). The ganglionic blocking agent, trimethaphan camphorsulfonate, administered to 6 patients by intravenous infusion, did not alter the heart rate but did diminish the cardiac output from 5.5 to 5.0 L./min./M.^{2} ($P < 0.01$).

Triiodothyronine administered to 1 patient with idiopathic orthostatic hypotension increased the pulse from 96 to 114 beats/min. and the cardiac output from 2.3 to 4.4 L./min./M.^{2}. Significantly, the basal metabolic rate increased from −7 to +25 during the same period.

These data strongly suggest that the sympathetic nervous system is not essential in producing the circulatory components of hyperthyroidism.

Severe Pulmonary Hypertension Secondary to Congenital Shunts in Adult Patients

Jose R. DeJesus, Jr., Ellet H. Drake, and Henry H. Gale, Detroit, Michigan

The study consisted of 25 patients with severe pulmonary hypertension secondary to atrial septal defect, ventricular septal defect, and patent ductus arteriosus. Ages ranged from 17 to 53 years. Right-heart catheterization was done on each patient and serially in 15. The pulmonary artery systolic pressure ranged from 80 to 130 mm. Hg and diastolic from 19 to 85 mm. Hg. Their resistance indices ranged from 5 to 28 units and femoral artery saturation from 60 to 96 per cent.

In atrial septal defect, there was a rise in pulmonary artery pressure of 10/5 mm. Hg and in patent ductus arteriosus 16/4 mm. Hg per year of observation, while in ventricular septal defect, there was no definite rise in pressure. However, there was diminution in volume of pulmonary flow and rise in pulmonary resistances. The explanation is probably that by the time these patients reach adult age, their pulmonary artery pressure has

reached its maximum, and the progressive diminution in the total vascular bed is responsible for the increase in resistances and fall in pulmonary blood flow.

While we were cognizant of the great risks involved in this group of patients, 17 were operated. Ten patients died in the immediate postoperative period, while 7 patients survived the operation. Two of them, an atrial septal defect and a patent ductus arteriosus, had persistence of severe pulmonary hypertension along with increasing incapacity that lasted for 3 years after surgery. Both showed advanced occlusive lesions of the pulmonary arterioles. Five patients with pulmonary blood flow at least twice the systemic had excellent results, their resistance indices ranging from 5 to 10 units. In 4 of them, a repeat catheterization 16 months later showed a drop in pulmonary artery pressure from an average level of 97/37 to 41/20 mm. Hg. In 8 cases, the risk of repair was considered too great, and they were followed medically for from 2 to 7 years. Conservative management with drugs failed to alter the progressive deterioration of pulmonary hypertension and resistance, although they had very little disability.

The pulmonary histology in 2 cases showed early changes in the arterioles with medial hypertrophy and slight intimal reaction. Their resistance indices were 5.4 units. In 8 patients, the advanced structural changes were associated with markedly elevated resistance indices of 13 to 20 units.

Effects of Intrarenal Infusion of Angiotensin in the Dog

Francesco del Greco, Chicago, Illinois, and Irvine H. Page, Cleveland, Ohio

Administration of natural angiotensin intravenously (I.V.) in the normal dog causes blood pressure (BP) rise, antidiuresis, and decreased renal plasma flow and filtration rate.

This study dealt with the effects of synthetic isoleucyl 5-angiotensin II (angiotensin II) on separate kidney function of normal, pentobarbital-anesthetized (60 mg./Kg. I.V.) dogs during moderate water diuresis. The ureters were exposed and cannulated. The main branch of the left renal artery (LRA) was exposed by translumbar approach. Femoral BP, excretion of water (V), chloride ($U_{Cl}V$), and total solute ($U_{Osm}V$), and water (C_{H_2O}) and creatinine clearances (C_{Cr}) were observed before and during sustained infusion of angiotensin II (0.4 to 1.4 μg./min.) in LRA and I.V. In certain experiments, the effects on BP alone after administration of angiotensin II into splenic and femoral artery (SA, FA) were also studied.

Angiotensin II infused in LRA decreased V, $U_{Cl}V$, $U_{Osm}V$, C_{H_2O}, and C_{Cr} of the left kidney but did not change BP or function of the right (control) kidney. BP also failed to rise when angiotensin II was given in SA and FA. By contrast, angiotensin II given I.V. increased BP and decreased kidney function bilaterally.

The absence of BP rise after angiotensin administration intra-arterially might be due to rapid dilution or inactivation or to inability to reach effector sites. Furthermore, angiotension may depress renal function independently of its effect on systemic BP.

Effects of Acidosis and Alkalosis on Fibrinolytic Parameters in the Dog

Stavros Deliyiannis, Hiromichi Tsuchioka, Samuel Bellet, George Tsitouris, Jean Schraeder, and Herschel Sandberg, Philadelphia, Pennsylvania

Previous studies have shown that various pathologic states are accompanied by alterations in fibrinolytic parameters. Since electrolyte imbalance frequently accompanies cardiac disease, we decided to study the effects of acidosis and alkalosis on fibrinolysis.

Metabolic acidosis was produced in dogs by 2 procedures: (1) the infusion of ammonium chloride intravenously over a 3-hour period, and (2) the infusion of fifth-normal hydrochloric acid. Metabolic alkalosis was achieved with the infusion of hypertonic sodium lactate. Respiratory acidosis was produced by administering 20 per cent CO_2 to the anesthetized animal. A control group was infused with physiologic saline. Serial blood samples were collected and analyzed for pH, serum sodium, potassium, chlorides, CO_2 combining power, and oxygen content, as well as for the following fibrinolytic parameters: lysis time of undiluted and diluted plasma, euglobulin lysis time, antifibrinolytic activity, and plasma fibrinogen concentration.

In the ammonium chloride-treated animals, a sharp decrease in fibrinolytic activity occurred, accompanied by an increase in antifibrinolytic activity. In the animals rendered acidotic by either HCl or the inhalation of CO_2, a marked increase in the fibrinolytic activity appeared. No significant changes were noted in the fibrinolytic parameters of the dogs treated with saline or those rendered alkalotic with sodium lactate.

These findings may have important clinical significance. Since the infusion of ammonium chloride produced anti-fibrinolytic activity, the possibility arises that this agent might be employed therapeutically to combat hemorrhagic diatheses complicating fibrinolytic therapy in certain thromboembolic states.

Reduction of Internal Work of the Heart by Left-Heart Bypass (P)

Clarence Dennis, Brooklyn, New York, David P. Hall, Augusta, Georgia, Juan Moreno, Cordoba, Argentina, and Åke Senning, Zürich, Switzerland

In order to evaluate the effect of left-heart bypass on cardiac oxygen utilization, a cannula was sutured into the coronary sinus, flow was determined by stopwatch and chemical balance, and arteriovenous oxygen differences were determined. Bypass took blood from the left atrium through a flowmeter and pump to the aorta.

With prolonged experiments, small changes in control oxygen utilization occurred, but these were magnified by air embolism, manipulation, blood pressure changes, and arterial unsaturation. With these factors controlled, bypass reduced oxygen utilization in each of 17 experiments below that of a non-bypass control performed temporally adjacent to it. The mean oxygen utilization with low bypass (below 61 ml./Kg./min.) was 0.25 ml./Kg./min., compared to 0.30 ml./Kg./min. for the paired controls. The mean oxygen utilization of all higher bypasses was 0.21 ml./Kg./min., compared to 0.33 ml./Kg./min. for paired controls.

With a transjugular, transseptal cannula, all blood returning to the left heart was shunted. During such bypass, the mean oxygen utilization was 0.19 ml./Kg./min., compared to 0.34 ml./Kg./min. for paired controls.

The mean of ratios of experimental oxygen utilization to paired control is significantly reduced by low bypass ($P < 0.001$). High bypass reduces it significantly below the level of low bypass ($P < 0.001$). With full bypass, it is significantly lower than any other group of 5 or more observations ($P < 0.001$).

Left atrial cannulation without thoracotomy permitted full bypass for 24 hours with survival of 9 of 10 dogs. Clinical use has begun.

Vascular Variations in Renal Ischemia Hypertension (P)

John R. Derrick and Donald C. Spencer, Galveston, Texas

The clinical counterpart of the Goldblatt kidney may take many forms, although all have in common renal ischemia. The concept of systemic hypertension secondary to renal ischemia is well accepted. Any of the possible causes of ischemia of the renal parenchyma may produce systemic hypertension by the formation of the pressor substance angiotensin. The kidney is divided into 5 distinct arterial segments, between which there is no appreciable anastomosis. Since aberrant renal arteries are truly segmental renal arteries with varying origins, it is logical to conclude that vascular insufficiency of an aberrant renal artery may produce segmental renal ischemia and subsequent systemic hypertension.

In a series of 22 patients operated on for hypertension of renal vascular origin, 6 patients were found to have hypertension on the basis of aberrant renal arteries. In 2 patients, congenital stenosis resulted in a decreased flow of blood to a segment of the kidney, whereas, in the rest of the cases, atheromatous deposition at the aortic takeoff of the aberrant renal artery was considered the cause of decreased blood flow to the segmental renal artery resulting in hypertension.

The diagnosis of patients with aberrant renal arteries using selective renal arteriography, pressure determinations of all segments of both renal arteries at the time of surgical exploration, and the surgical treatment and follow-up of patients with aberrant renal arteries were included in the study.

Experimental Considerations of Segmental Renal Artery Arteriography

John R. Derrick, Donald C. Spencer, Robert N. Cooley, and Richard W. Brown, Galveston, Texas

Five groups of animals were used to investigate the renal vascular lesions that may be demonstrated by arteriography.

Segmental renal arteries were ligated in 5 dogs, and percutaneous retrograde arteriograms were done to determine if the segmental ischemia could be demonstrated radiographically. Not only was the ligated branch demonstrated, but the parenchyma distal to the point of occlusion was not visualized, as was the remainder of the renal parenchyma.

An attempt was made to demonstrate subsegmental artery ligations arteriographically. However, it was soon apparent that these vessels were too small to be demonstrated well on x-ray; the area of parenchyma involved was so small that there was no radiographic change in the parenchymagram, and thus, the procedure was abandoned.

Unilateral vertical wedge resections were done on 5 dogs, and percutaneous retrograde arteriograms were done immediately postoperatively and again in 4 to 6 weeks. The early films revealed little change while the follow-up films revealed a loss of renal cortex and a "fussy" appearance of the parenchymagram.

Figure-of-eight sutures were placed in large portions of the renal cortex in 5 animals. Percutaneous retrograde arteriograms were done in the early postoperative period revealed no change when compared with the opposite kidney, while

follow-up films several weeks later revealed a "fussy" appearance at the point where the suture was placed.

Hemodilution Perfusions for Open-Heart Surgery (P)

Richard A. DeWall, Minneapolis, Minnesota*

A series of patients, representing virtually all types of congenital heart disease, have been given perfusions during open cardiac surgery utilizing a hemodilution principle, moderate generalized hypothermia, and minimal perfusion rates.

The oxygenator is primed with one-third of the patient's daily fluid requirement, using 5 per cent dextrose or low molecular weight dextran. No blood is used. Mixing this with the patient's blood volume does cause some hemodilution, which is to the patient's advantage since the diluted blood has a lower viscosity than whole blood and, consequently, he receives a better tissue perfusion at the hypothermic temperatures employed. The ability of low molecular weight dextran to prevent sludge flow is well recognized and also serves to advantage. Since moderate hypothermia is used, the patient's oxygen requirements are reduced to one-half or one-third of normal, and consequently, a perfusion rate of 30 cc./Kg. body weight generally seems to fulfill the oxygen needs. An efficient heat exchanger is used which does not require perfusion fluid separate from the pump-oxygenator and, therefore, serves to conserve blood volume.

After the perfusion, the contents of the oxygenator are returned to the patient, restoring his preoperative blood volume and one-third of his daily fluid requirement. The patients tolerate the increased water load well and rapidly absorb or excrete it. Also they have received only a minimum amount of foreign blood and are saved from some of the dangers of massive blood replacement.

Hemodynamic Correlates of the First Heart Sound (P)

Giuliano Di Bartolo, David Nunez-Dey, Chicago, Illinois, Giulio Muiesan, Pisa, Italy, Donald M. MacCanon, and Aldo A. Luisada, Chicago, Illinois

The temporal relationship between the "crossing" of equisensitive atrial and ventricular pressure tracings and the initial components of the first heart sound of the homolateral intracardiac phonocardiogram was analyzed in 35 dog experiments. These studies showed that the first component of the first heart sound followed the atrioventricular valve closure (AV crossing) in all instances by an average time interval of 23 msec. and that, at the time of its occurrence, there was a ventricular-atrial pressure gradient of 5 mm. Hg in the right side and 14 mm. Hg in the left side of the heart. It is concluded that valvular closure per se does not cause the first component of the first heart sound. Actually, the first heart sound occurs later, during the period of isometric ventricular contraction, suggesting that the rise of ventricular pressure is responsible for its vibrations. Comparative analyses of right and left intracardiac and external phonocardiograms showed that the right-side component of the first heart sound follows the left in about three-fourths of the cases and is coincident with it in the remainder, and that these events are reflected in the same order in the external phonocardiogram.

Late Effects of Mitral Commissurotomy on the Central Circulation

Donald W. Dickhaus and Elliot Rapaport, San Francisco, California

Fourteen patients with mitral stenosis, who had pulmonary vascular pressure, flow, and resistance measurements during and immediately after mitral commissurotomy 2 to 4 years ago, have been restudied by cardiac catheterization. In 9 there is evidence of residual mitral valve obstruction at rest and, in 5, only when cardiac output is increased by exercise. Three patients have clinical and catheterization evidence to suggest that mitral insufficiency now dominates the stenosis. Hemodynamic findings in 4 patients strongly suggest that mitral valve restenosis has occurred. The pulmonary vascular resistance in these patients failed to fall immediately after valve fracture. The pulmonary vascular resistance is still at the same high level in 6 patients, despite the fact that 2 have normal resting pulmonary artery wedge pressures at present. Five patients with normal resistances initially have remained normal. The 3 remaining cases demonstrated a significant late fall in pulmonary vascular resistance to normal, although 1 patient had a strikingly abnormal resting pulmonary artery wedge pressure.

It is concluded that the marked subjective improvement generally observed is disproportionate to the objective hemodynamic findings which suggest restenosis or the production of significant mitral insufficiency in half of these cases. Furthermore, the late response of the pulmonary vascular resistance has failed to correlate with the presence or absence of left atrial hypertension, and a significant fall was observed in only 3 of the 9 cases in which resistances were elevated initially.

Effect of Prolonged Streptococcal Prophylaxis on Quiescent Rheumatic Heart Disease

Antoni M. Diehl, Kansas City, Kansas, Athene L. Dale, Kansas City, Missouri, and Tom R. Hamilton, Kansas City, Kansas

One hundred and forty-six children with inactive rheumatic heart disease maintained on a continuous prophylactic program of intramuscular benzathine penicillin G, 1.2 million units every 28 days, for 1 to 8.5 years were studied. Comparison was made of auscultatory findings, cardiac fluoroscopy, and electrocardiograms taken initially and at termination of study. Average length of time on the study per child was 3 years and 10 months with 566 patient-years of observation. Initial age of patients was 12 years and, at termination of study, 16 years.

Of 135 initial apical murmurs, the intensity was unchanged in 52, increased 1 grade (1 to 6) in 22, and 2 grades in 1 instance. Decrease of 1 grade occurred in 42, 2 grades in 18, and 3 grades in 1. Disappearance occurred in 21. A new apical systolic murmur appeared once. Of 105 initial apical diastolic murmurs, 11 were unchanged. In 15, the intensity decreased 1 grade and, in 8 instances, 2 grades. Increase of 1 grade occurred 26 times, 2 grades 7 times, and 3 grades once. Apical diastolic murmur disappeared in 16; a new murmur appeared in 21 instances.

Transverse diameter remained fluoroscopically unchanged or decreased in 119 and increased in 27. Left ventricle size was unchanged or decreased in 111 and increased in 35. Right ventricle size increased in 10 and was unchanged or smaller in 136. Left atrial size increased in 19 and remained unchanged or decreased in 127.

Of 53 electrocardiograms showing initial left ventricular hypertrophy, there was an increase in 24, decrease in 6, and no change in 23. Right ventricular hypertrophy increased in 2, decreased in 3, appeared in 2, and disappeared in 3. Left atrial overloading increased in 10 of 39, decreased in 17, was unchanged in 12, and appeared in 8.

Continuous prophylaxis against streptococcal disease in rheumatic heart disease appears to influence favorably the magnitude of cardiac damage. Prediction as to prognosis in individual cases is not possible.

Blood Volume and Respiratory Distress in the Neonate —A Preliminary Report

Herman A. Dobbs, Jr., Robert R. Franklin, Walter S. Henly, and Murdina M. Desmond, Houston, Texas*

Blood volume determinations, using Evans blue dye and a spectrophotometric correction for plasma turbidity and hemolysis, have been performed on 21 newborn infants during the early hours of life (the majority within 1 hour of birth). The subjects were followed carefully for signs of respiratory distress in a special nursery. Of 11 term infants born by the vaginal route, 9 had no respiratory distress, and these had an average blood volume of 128 ml./Kg. (range 65 to 182 ml./Kg.). Two exhibited mild distress; these had an average blood volume of 61 ml./Kg. (57 and 67 ml./Kg.). Of 2 term infants born by cesarean section, 1 had a normal course and a blood volume of 88 ml./Kg.; the other showed mild respiratory distress and had a blood volume of 63 ml./Kg. Thus, the average blood volume of the 3 distressed babies (62 ml./Kg.) was half that of the 10 normal infants (124 ml./Kg.).

On the other hand, in 8 premature infants, there was no correlation between blood volume and the occurrence of respiratory distress.

Left Ventricular Pressure-Volume Loops in Man with Valvular Heart Disease (P)

Harold T. Dodge, Harold Sandler, and Robert E. Hay, Seattle, Washington

Left ventricular (LV) pressure-volume (P-V) loops have been determined in 14 human subjects with mitral and/or aortic valvular disease. LV volumes (LVV) were calculated and LV volume curves constructed from biplane angiocardiograms taken at 6 per second and timed with respect to the heart cycle. P-V loops were determined by relating LV pressure (LVP) and volume. Marked differences in shape and size of individual P-V loops are due primarily to differences in type and severity of valvular lesions. Location of individual P-V loops on the volume axis seems to reflect the state of myocardial compensation. From the P-V loops, 3 types of LV work were calculated: (1) LV systolic work,

$$\int_{V_S}^{V_D} P_s \, dV \quad (P_s = \text{systolic LVP}),$$

area beneath the systolic portion of the curve; (2) work done on the diastolic LV,

$$\int_{V_S}^{V_D} P_D \, dV \quad (P_D = \text{diastolic LVP}),$$

area beneath the diastolic portion of the curve; and (3) net LV stroke work, $\oint PdV$, LV systolic work minus work done on the LV in diastole. Net LV work varied from 56 to 457 Gm. M./beat in differing valvular lesions. Work performed in distending the diastolic LV was as much as 79 Gm. M./beat. LV P-V loops provide the only method at present for measuring these features of LV work.

Tritiated Digoxin Serum Turnover Rates After Cardiopulmonary Bypass (P)

James E. Doherty, Masauki Hara, Ben M. Lincoln, and William H. Perkins, Little Rock, Arkansas

Decreased tolerance to digitalis glycosides has sometimes been noted in patients subjected to cardiopulmonary bypass for correction of intracardiac defects.

Tritium-labeled digoxin was utilized to study blood serum turnover rates of mongrel dogs after 30 minutes of cardiopulmonary bypass. A single dose was administered intravenously immediately after surgery. A control study was done either before or several weeks after the bypass. Seventeen dogs were studied by this method. Complete data were obtained on 11 animals.

Serum levels of radioactivity plotted on semilogarithmic graph paper demonstrated 2 exponential curves: (1) an early, rapidly disappearing curve, representing distribution and tissue fixation of digoxin, and (2) a late, dominant curve, representing metabolism and excretion.

The mean half-time (T ½ or time required for one-half of the radioactivity originally present to disappear from the serum) of the early curve was 11 minutes after the bypass, while that of the control study was 20 minutes ($P < 0.01$). The second or late curve was prolonged on the bypass study with a mean T ½ of 3,414 minutes, while that of the control group demonstrated a more rapid turnover rate, 1,700 minutes ($P < 0.05$).

The data demonstrate a statistically significant difference in turnover rates and thus, presumably, a difference in the manner in which digoxin was metabolized after cardiopulmonary bypass.

Flow-Guided Cardiovascular Catheterization

Charles T. Dotter and Kurt R. Straube, Portland, Oregon

The use of flexible tubing permits "blind" right heart catheterization by taking advantage of the patient's blood flow. The approach obviates the manipulation under fluoroscopy required to position conventional cardiac catheters, since catheter location is readily recognized manometrically. This technic promises to provide a simple means for ward or office determination of the pulmonary artery pressure in the routine work-up of cardiovascular patients. Cutdowns are not required, inasmuch as the tubing is introduced into veins through a needle and into arteries through the lumen of percutaneously inserted polyethylene tubing. With the latter positioned appropriately, a protruding short length of highly flexible inner tubing is readily maneuvered into previously inaccessible vessels, such as branches of the internal carotid, coronary, renal, and celiac arteries. Experimental and clinical evidence indicates the technic is safe, easily learned, and highly useful. It has led to collateral study of byproducts such as "captive," i.e., tethered, right-heart transducers injected into and recovered from peripheral veins.

Cigarette Smoking and Coronary Heart Disease: Combined Albany-Framingham Study (P)

Joseph T. Doyle, Albany, New York, Thomas R. Dawber, William B. Kannel, Framingham, Massachusetts, A. Sandra Kinch, Albany, New York, and Harold A. Kahn, Framingham, Massachusetts

Although the relationship between cigarette smoking and death from coronary heart disease (CHD) has been previously demonstrated, insufficient data have been available to relate cigarette smoking to morbidity from CHD. Accordingly, a combined study was undertaken relating cigarette smoking to development of CHD in 2 population groups: male civil servants aged 39 to 55 (Albany) and a general population group aged 30 to 59 (Framingham). The development of CHD in these populations has been determined, using uniform criteria for CHD and smoking categories. Ratios of observed to expected cases of CHD developing in males under observation in the 2 studies were computed. These morbidity ratios were analyzed separately for each study and in combination.

In each study, cigarette smoking was associated with an increased risk of development of myocardial infarction and death from CHD. Neither study showed a relationship of cigarette smoking to the development of angina pectoris, nor did combination of the data demonstrate any relationship.

The standardized morbidity ratios for myocardial infarction in the 2 studies were significantly higher for cigarette smokers than for noncigarette smokers. The risk of developing myocardial infarction was very similar in those who had never smoked, smoked cigars or pipe only, or had given up smoking. Heavy cigarette smokers ran over 3 times the risk of developing myocardial infarction or dying of CHD, as compared with noncigarette smokers. The effect of cigarette smoking was independent of blood cholesterol level, blood pressure, and weight.

Simultaneous Recording of Intracardiac Pressures, Intracardiac Phonocardiogram, and Simultaneous Average Pressures

Ellet H. Drake, Detroit, Michigan, and Alan Warnick, Dearborn, Michigan

An improved system has been developed for monitoring cardiac physiologic phenomena which permits recording of intracardiac pressure curves, simultaneous average pressures, a selective intracardiac phonocardiogram, and both intracardiac and conventional electrocardiograms. One of the intracardiac transducers tested in the system is a

low-resistance (100 ohm) version of 2 improved models of the scientific laboratory's transducer. The available power sensitivity has been increased by a factor of 9.2 by replacing the strain gauge windings with bonded metal foil strain gauges. The natural frequency of this transducer is 2,000 c.p.s., and the noise with a 20-KC carrier system having a 2,000 c.p.s. cutoff is equivalent to 0.1 mm. Hg. A series of static calibration tests on selected transducers shows a reproducibility of 1 per cent with a total deflection of 100 mm. Hg. The characteristics of the high-resistance transducer (2,000 ohm) are similar, and the voltage output of 18 μv. per mm. Hg is sufficient for modern D.C. amplifiers. As a result of the high sensitivity and frequency response, any part of the frequency range to 2,000 c.p.s. may be selectively filtered and subjected to additional amplification for recording the intracardiac phonocardiogram.

By utilizing the catheter lumen, an average pressure is continuously recorded through an extracardiac transducer. The metal shell of the catheter tip sensing unit is employed as an exploring electrode for a unipolar intracardiac electrocardiogram, or the conventional leads may be recorded. The metal catheter tip and the presence of lead wires in the wall give the catheter unique manipulative properties. Blood sampling is from the tip at the exact site where pressures are monitored. Recording of the phasic pressures by intracardiac transducer gives a curve free from acceleration effects and other motion artifacts.

Serious Cardiac Arrhythmias Following Acute Myocardial Infarction

Leonard S. Dreifus and William Likoff, Philadelphia, Pennsylvania

A high immediate mortality has been associated with acute myocardial infarction in the presence of cardiac arrhythmias.

Review of 370 consecutive acute myocardial infarctions revealed 53 instances in which there was an associated serious cardiac arrhythmia. Of this group, 20 died with their arrhythmia.

Atrial arrhythmias were associated with a 47 per cent immediate mortality (9 cases) as opposed to 27 per cent with uncomplicated myocardial infarction. Digitalis or its glycosides were unquestionably the drugs of choice for these arrhythmias.

Ventricular tachycardia was associated with a 60 per cent immediate mortality (11 cases) in spite of antiarrhythmic therapy. Failure to respond to procaine amide was a poor sign since other agents (quinidine, KCl, and lidocaine) were invariably ineffective. However, if the patient survived the initial complication, long-term survival was equally as good as in those with an uncomplicated infarction.

Mortality increased with the magnitude and persistency of A-V block. Isoproterenol enhanced impulse formation in incomplete A-V block by acceleration of supraventricular pacemakers as well as by improvement of A-V conduction. Steroids were successful in a few instances of transitory A-V heart block. Advanced second and third degree A-V block should be continuously monitored because of instability of subsidiary pacemakers. An electrical pacemaker should be available to initiate impulse formation after 5 seconds of asystole.

Nonparoxysmal nodal tachycardia may masquerade as a simple supraventricular arrhythmia. Inappropriate use of digitalis may permit the patient to die with this rhythm. Successful treatment appears to be related to early identification of simple arrhythmias, which are frequently associated with more complex mechanisms, and an aggressive approach to cardiac resuscitation.

Serious Cardiac Arrhythmias Induced by Digitalis: Prognosis and Management

Leonard S. Dreifus, William Likoff, and Sheldon R. Bender, Philadelphia, Pennsylvania

Certain cardiac arrhythmias associated with digitalis toxicity appear intractable to therapy, while others exhibit forewarning mechanisms and enjoy a less sinister prognosis.

This study included 100 consecutive patients developing serious cardiac arrhythmias during digitalization, following supplemental administration, or subsequent to intensive diuretic therapy in digitalized individuals. Patients with only frequent or multifocal premature ventricular beats were excluded.

Withholding of digitalis and the administration of potassium or procaine amide was successful in 16 of 20 (80 per cent) patients with paroxysmal atrial tachycardia (PAT) with block; in 32 of 37 (87 per cent) patients with high-grade A-V block associated with a passive nodal or ventricular pacemaker; in 11 of 26 (40 per cent) patients with nonparoxysmal nodal tachycardia; and in 2 of 11 (18 per cent) cases of continuous ventricular tachycardia. In 4 of 6 (67 per cent) other cases of intermittent ventricular tachycardia (group beating of no more than 4 ectopic ventricular complexes), therapy was successful.

The following observations were made: (1) Although 34 patients died, mortality was concentrated among those with continuous ventricular tachycardia (9 cases) and nonparoxysmal nodal tachycardia (15 cases). (2) Nonparoxysmal nodal tachycardia frequently was not recognized as a

manifestation of digitalis excess, and subsequent digitalis was futilely administered. (3) Failure to treat patients with high-grade A-V block with passive lower pacemakers invariably engendered nonparoxysmal or ventricular tachycardia. (4) Serum potassium was 3.5 mEq. or less in only 9 of 50 cases. (5) Procaine amide appeared to be equally as effective as potassium in treating nonparoxysmal nodal tachycardia and intermittent ventricular tachycardia. Withholding digitalis sufficed for passive nodal rhythms, while PAT with block usually required I.V. potassium.

Response to Methoxamine in Two Different Hemodynamic States

Martin Duke, Richard P. Ames, and Walter H. Abelmann, Boston, Massachusetts

Six healthy subjects (mean age 36) with normal cardiac output and 3 patients (mean age 35) with elevated cardiac output and decreased peripheral resistance associated with severe anemia (hemoglobin 5.8 Gm./100 cc.) received methoxamine intravenously, 8.5 to 20.7 mg. at 0.3 to 0.6 mg./min. In normals, heart rate decreased 21 per cent from 66 beats/min., mean arterial pressure rose from 97 to 118 mm. Hg, and total systemic resistance increased 27 per cent from 1,068 to 1,357 dynes/sec./cm.$^{-5}$. Cardiac index (dye-dilution) averaged 4.0 L./min./M.^{2} and showed no consistent change, while stroke index, averaging 60.3 cc./beat/M.^{2}, rose in all but 1 case, a mean change of 27 per cent. In patients with elevated output, heart rate fell 34 per cent from 89 beats/min., mean arterial pressure increased from 82 to 91 mm. Hg, and total systemic resistance rose 41 per cent from 719 to 1,015 dynes/sec./cm.$^{-5}$. Cardiac index fell 24 per cent from 6.2 to 4.7 L./min./M.^{2}. Stroke index, averaging 71.3 cc./beat/M.^{2}, fell in 1 case and rose in 2.

The normal, in response to methoxamine-induced bradycardia and increased peripheral resistance, raised stroke volume and usually maintained cardiac output. On the other hand, in the high-output state associated with anemia, stroke volume failed to compensate for the induced bradycardia and increased peripheral resistance, and cardiac output uniformly decreased. It appeared that when initial cardiac and stroke index were elevated, methoxamine showed the greatest tendency to lower cardiac output.

Effect of Chlorothiazide on Cardiac Output Responses to Norepinephrine (P)

John W. Eckstein, Santiago A. Pereda, Francois M. Abboud,† and Michael G. Wendling, Iowa City, Iowa*

In previous experiments, increasing doses of norepinephrine were associated with progressive decreases in forearm blood flow. The same subjects responded to the same doses of norepinephrine with progressive increases in flow after 1 week of treatment with chlorothiazide. These observations led to the speculation that chlorothiazide might alter the effect of norepinephrine on cardiac output.

Cardiovascular responses to graded doses of norepinephrine were measured in 12 dogs anesthetized lightly with thiopental and decamethonium. Six had been treated with chlorothiazide, 25 mg./Kg./day for 7 days. Six were untreated. All had received water *ad libitum* and the same diet (based on body weight) for 7 days. Norepinephrine base was infused intravenously at rates of 0.1, 0.2, and 0.4 μg./Kg./min. Each dose was repeated in each animal. The other of infusion was randomized both in treated and untreated groups using the same 6 × 6 Latin square. Observations were made immediately before and after 2½ minutes of norepinephrine infusion.

Cardiac output did not change appreciably, but arterial pressure and peripheral resistance increased significantly with increasing doses of norepinephrine in untreated dogs. Treated dogs had significant increases in cardiac output but only slight increases in peripheral resistance. The changes in arterial pressure were about the same in the 2 groups.

Progressive increases in cardiac output with increasing doses of norepinephrine were observed in dogs treated with chlorothiazide. Norepinephrine had no significant effect on cardiac output in the untreated dogs.

Determination of Blood Flow in the Human Limb by Dye-Dilution Method (P)

Edward A. Edwards and Giorgio Agrifoglio, Boston, Massachusetts

Blood flow in the limb can be determined from the dye-dilution curve of blood withdrawn from the femoral vein after injection of I^{131}-labeled human serum albumin into the companion artery. Continuous venous sampling over 2½ minutes was divided into 5-second collections. The radioactivity of the samples reached a peak, then declined in the expected exponential manner. Flow was calculated from the concentration/time curve by means of the Stewart-Hamilton formula. The flow was related to limb volume, as measured by displacement in a tank. Results were reproducible in repeated tests in the same individuals.

Total limb flow in normal subjects ranged from 450 to 886 ml./min. (6.30 to 7.78 ml./min./100

ml. limb volume); in vasospasm 447 to 566 (5.38 to 5.77); in arteriosclerosis with occlusion below the popliteal artery 316 to 669 (4.56 to 5.72); and with femoro-popliteal occlusion, with or without partial aorto-iliac disease, 143 to 432 (2.24 to 4.79); and in a case of myxedema 255 (ca: 3.40).

The flow in arteriosclerotic patients with favorable clinical effects after sympathectomy was increased in a range of 30.5 to 74.6 per cent above their preoperative values and in a patient with probable scleroderma by 36.5 per cent.

Reserpine therapy in one patient with chronic vasospasm increased flow by 32.2 per cent.

Clinical Evaluation of a Potentiometric Electrode for the Diagnosis of Left-to-Right Shunt

F. Kathryn Edwards, Robert C. Schlant, Thorne S. Winter, III, Wade H. Shuford, and William E. Long, Atlanta, Georgia

In an attempt to evaluate the clinical use of the potentiometric method of detecting intracardiac shunts described by Clark and Bargeron, a special catheter with a platinum band electrode 1.6 mm. proximal to a single-end opening (U.S. Catheter & Instrument Corp., modified 353) has been used. During routine diagnostic cardiac catheterization, this catheter can be used to secure the usual samples and pressures for analysis. In order to determine the ability of the potentiometric method to detect a shunt and to compare its sensitivity, we have obtained potentiometric curves using hydrogen inhalation as an indicator and simultaneous samples for Van Slyke analysis during a standard diagnostic run.

This catheter has been used in over 100 routine right-heart catheterizations and has been found to be as accurate as routine determinations for indicating the level of shunt. Detailed data from 30 complete diagnostic runs are available in which simultaneous potentiometric and oxygen determinations were obtained. These revealed a sharp appearance time of from 0.5 to 2 seconds from the time of inhalation of hydrogen in patients with a left-to-right shunt. In one-fourth of these cases, the potentiometric method accurately indicated a shunt, whereas the oxygen content was not great enough by currently accepted standards to be diagnostic.

The observations of Bargeron and Clark that the platinum electrode is also sensitive to potential changes due to pO_2, were confirmed, and when used to indicate that the catheter tip has entered a chamber of higher pO_2, this fact will aid in directing the catheter across defects.

Calcific Aortic Stenosis—An Effective Surgical Treatment

Donald B. Effler, Laurence K. Groves, F. Mason Sones, Jr., and Earl K. Shirey, Cleveland, Ohio

Surgical treatment of acquired aortic stenosis predates the era of open-heart surgery. The blind transventricular and supravalvular approaches that utilized finger, knife, or mechanical dilators are obsolete. Advantages of the direct approach offered by extracorporeal circulation and adjunctive cardiac arrest are obvious.

Careful preoperative study by left-heart catheterization and complementary coronary arteriography affords a rational basis for selection or exclusion of candidates for surgery. Evaluation of coexisting coronary arterial disease is mandatory; surgical relief of valvular stenosis accomplishes little in the presence of severe coronary insufficiency.

A surgical technic has been evolved from 6 years' experience with extracorporeal circulation. The excellent exposure of the aortic valve and its related structures, plus freedom of motion, fulfill requirements for the ideal surgical field. Cardiac arrest is produced by regional hypothermia and maintained with a temperature level between 12 and 18 C. Quinidine sulfate, administered in the precooling phase, facilitates restoration of effective heart beat.

Whereas initial inspection of the severely calcified valve may be discouraging, we are now convinced that the majority can be salvaged by painstaking decortication and selective commissurotomy. Clinical success, however, demands unlimited time and determination.

Experience with 75 patients who were operated on for calcific aortic stenosis proves that this method of therapy may be applied to seriously ill patients regardless of age. The oldest survivor in this series is a 74-year-old man; there are 4 patients over 62 years of age. We believe that prosthetic replacement should be reserved for patients who cannot be helped by decortication and commissurotomy.

Muscular Subaortic Stenosis in Glycogen Storage Disease of the Myocardium

Kathryn H. Ehlers, Jack W. C. Hagstrom, Daniel S. Lukas, S. Frank Redo, and Mary Allen Engle, New York, New York

The massive left ventricular hypertrophy characteristic of cardiac glycogen storage disease might be expected to produce obstruction to left ventricular outflow. This concept was proved physiologically and confirmed pathologically in a 9-month-old infant. He presented in heart failure with

a murmur of aortic stenosis and with electrocardiographic changes suggestive of glycogen storage disease as the cause of his marked left-sided cardiomegaly. Left-heart catheterization demonstrated a systolic pressure of 255 mm. Hg in the left ventricle and 97 mm. Hg in the simultaneously recorded femoral arterial tracing. The form of the tracings indicated muscular subaortic stenosis since there was no obstruction to ejection early in ventricular systole, but a striking gradient developed as systolic contraction progressed. An attempt to relieve the muscular obstruction at open-heart surgery was unsuccessful. Systolic narrowing of the subvalvular tract was apparent through the aortotomy. At necropsy, the enormously thickened myocardium of the left ventricle bulged into the outflow tract. Deposition of large amounts of structurally normal glycogen was demonstrated in heart muscle and other tissues by appropriate staining technics and biochemical analysis.

Review of 54 reports of pathologically proved cardiac glycogenosis revealed several features which should permit diagnosis during life of the cardiac form of this error of cardiac metabolism. This is the first such infant diagnosed during life who was studied by left-heart catheterization and at operation and proved to have severe muscular subaortic stenosis. Conversely, this is 1 of the few patients with functional subaortic stenosis of known etiology.

Effects of Digitalis in Patients Receiving Reserpine

Lee Ehrlich, Phoenix, Arizona, Bernard Lown, Boston, Massachusetts, Bernard Lipschultz, Phoenix, Arizona, and John Blake, Sacramento, California

Fifteen patients in congestive heart failure, all of whom were receiving maintenance doses of digitalis, were studied for sensitivity of the myocardium to acetyl strophanthidin both immediately before and during the administration of reserpine.

In patients with atrial fibrillation, reserpine increased the toxic action of digitalis, as indicated by a marked increase in the incidence of arrhythmias. While 8 out of 9 patients in atrial fibrillation who were receiving reserpine developed advanced toxic rhythms during acute digitalization, only 1 patient responded in this fashion when reserpine was not given. The patients on reserpine were unable to tolerate full doses of acetyl strophanthidin.

The mechanism by which reserpine predisposes to ventricular ectopic beats is unknown. The fact that potentiation of digitalis action by reserpine was observed only in patients in atrial fibrillation suggests that advanced heart disease is a requirement for this interaction.

Reserpine increases cardiac sensitivity to carotid sinus stimulation irrespective of the heart rhythm and was most marked in patients receiving digitalis as well. Reserpine did not prevent significant acceleration of the ventricular rate following exercise.

Orthostatic Alterations in Blood Volume in Normal Subjects and Patients with Congestive Heart Failure

Seymour Eisenberg and Mary F. Camp, Dallas, Texas

In normal subjects, assumption of the erect posture is associated with a significant decrease in intravascular volume. This, together with pooling of blood in dependent parts, is undoubtedly responsible for the decline in cardiac output associated with standing. The purpose of this study was to determine whether these changes in volume were altered in patients with congestive heart failure and whether an abrupt increase in vascular volume might not be responsible for orthopnea when the patients resumed the recumbent posture.

Blood volume alterations in 10 edematous persons with cardiac decompensation were studied utilizing Cr^{51}-tagged red cells or I^{131}-tagged albumin (RISA). With standing for 20 minutes, there was a mean decrease in blood volume of 420 ml. On resumption of the recumbent posture, the blood volume returned to normal after 20 minutes. Moreover, after 40 to 60 minutes, there was a distinct "overshoot," the blood volume exceeding the control recumbent value by 100 to 300 ml.; in many subjects, this was associated with an increase in the severity of their respiratory discomfort. The changes in hematocrit and plasma proteins and the RISA values indicate that these alterations were confined to the plasma space.

It is suggested that the abrupt expansion of the blood volume in persons with cardiac decompensation is largely responsible for the dyspnea they experience with recumbency.

Effects of Vagal Stimulation and Acetylcholine on the Ventricle: Studies in Dogs with Complete A-V Block

Marcel Eliakim, Samuel Bellet, Elias Tawil, and Otto F. Muller, Philadelphia, Pennsylvania

Data on the direct effects of vagal stimulation and acetylcholine on the ventricle of the living animal are scarce and controversial. This study was designed to obtain information on the role of these stimuli in the ventricular performance of dogs with experimentally produced complete A-V block.

Electrical vagal stimulation was found to cause slowing of the ventricular rate in 9 out of 23 experiments in 8 dogs with experimental complete

A-V block. Acetylcholine (20 to 500 μg./Kg.) produced various degrees of bradycardia in 21 of 22 experiments and a decrease in the force of ventricular contraction in 14 out of 22 experiments in 8 dogs. A slight increase in ventricular rate and force of contraction followed the initial cardioinhibitory phase in about half of the cases. The cardioinhibitory effects were enhanced by neostigmine and abolished by atropine. Phentolamine abolished the cardiostimulating effects of the larger doses of acetylcholine. Acetylcholine caused slowing of the ventricular rate in 5 dogs with complete A-V block and ventricular tachycardia produced by digitalis or aconitine and effected reversal to sinus rhythm in 2 out of 3 dogs with normal atrioventricular conduction and ventricular tachycardia produced by aconitine.

These results indicate that vagal influences may possibly play a role in the regulation of the spontaneous changes of ventricular rate in patients with complete A-V block. Furthermore, acetylcholine, even in the absence of an intact vagal innervation, may alter the ventricular rate and the force of ventricular contraction in complete A-V block.

Is There A Senile Heart? Its Relation To Coronary Artery Disease

Laurence B. Ellis, Robert B. Allison, and Felix L. Rodriguez, Boston, Massachusetts

There has been some question raised as to whether heart disease and failure as seen in aging persons can be assumed to be due to the effects of coronary artery disease (CAD), provided other identifiable causes are not present, or whether there is such an entity as the "senile heart" due to other factors. The present clinical-pathologic study is based on 430 unselected postmortem examinations with injection of the hearts by the Schlesinger technic. After excluding patients with chronic arterial hypertension or valvular disease, there were 221 remaining, with an average age at death of 67 years, of which 65 had had chronic congestive failure. In these 65, chronic anemia, severe pulmonary disease, or old myocardial infarctions occurred in all but 1 of 27 patients with 0 to 2 plus CAD and in 10 of 15 with 3 plus CAD, but anemia or pulmonary disease did not occur in the 23 with occlusive CAD (22 with old infarctions).

In the group of 221, cardiac hypertrophy was found in 21 per cent of 146 cases without occlusive CAD or failure, in 87 per cent of 23 with occlusions and failure, and in 60 per cent of those with either occlusions or failure. Thus, occlusive CAD (or myocardial infarctions) and chronic heart failure are each associated with the occurrence of cardiac hypertrophy.

It is concluded that chronic congestive failure in our hospital population can be considered to be due almost always to severe coronary artery disease, usually with myocardial infarction, if hypertension, valvular disease, chronic pulmonary disease, or severe chronic anemia can be excluded.

Arterial Embolization in Relation to Mitral Valvuloplasty

Laurence B. Ellis and Dwight E. Harken, Boston, Massachusetts

The purpose of this study has been to define the conditions under which peripheral arterial embolization takes place, based on our experience with 1,500 consecutive patients with predominant mitral stenosis on whom valvuloplasty was performed. Atrial fibrillation, increasing severity of heart disease, and the occurrence of preoperative embolization all increase the risk of operative embolization. Embolization within 8 weeks of surgery carries a higher risk of operative embolization than if an embolus occurs earlier.

In patients receiving preoperative anticoagulant therapy, usually for a short period and stopped some days prior to surgery, there was no protection against operative embolization.

Our present findings confirm those previously reported by us in respect to the protective value of mitral valve surgery against future embolization. Late postoperative emboli have occurred in 38 patients out of the entire group followed for a mean period of 6 years, an incidence of 0.5 per cent per patient year. This is a very much lower figure than the expected incidence, based on the reports of others, of embolization in patients of this type. The increased risk of operative embolization in certain patients is about balanced by the increased hazard of recurrent spontaneous embolization in the same categories of patients. The increased risk of operative embolization if surgery is carried out within 8 weeks of the embolic event is also canceled out by the possibility of a recurrent embolus within this period if followed medically.

On the basis of these findings, mitral valvuloplasty is indicated in patients with mitral stenosis who have had a peripheral embolus, even without significant cardiac disability, as a protection against future emboli.

Significance of Fever in Patients with Rheumatic Heart Disease (P)

Samuel K. Elster, Elmer Pader, and Henry Horn, New York, New York

Persistent fever, often associated with cardiac failure, occurs commonly in patients with rheu-

matic heart disease. In order to define the causes of such fever and to determine distinguishing clinical features which will permit proper antemortem diagnosis, a clinical-pathologic study was conducted in 60 such subjects. At necropsy, 7 major entities were delineated: (1) pulmonary infarction (31 patients), usually multiple, including 9 patients with associated systemic infarction; (2) "active" rheumatic heart disease (12 patients), based on the presence of numerous myocardial Aschoff bodies; (3) bronchopneumonia (6 patients); (4) congestive heart failure alone, without evidence of thromboembolism, infection, or "activity" (5 patients); (5) subacute bacterial endocarditis, unrecognized antemortem and with sterile blood cultures (3 patients); (6) pulmonary arteritis, characterized by severe diffuse necrotizing arteritis of the pulmonary vasculature (2 patients); and (7) systemic embolism with infarction (1 patient).

Although no uniform distinguishing clinical characteristics were uncovered, hemoptysis, chest pain, and clinical jaundice were more common in the "pulmonary infarction" group, whereas those in the "active" group were younger, had a higher incidence of regular sinus rhythm, and mostly had elevated ASO titers. Other laboratory, x-ray, and electrocardiographic findings were not diagnostic. Response to treatment was unavailing and unrevealing, despite the use of anticoagulants, antibiotics, salicylates, and adrenocortical hormones.

This study calls attention to the frequent, related fatal complications of rheumatic heart disease in the adult, such as pulmonary infarction, and emphasizes the importance of recognition of less common causes, such as heart failure alone, necrotizing pulmonary arteritis, and active Aschoff lesions in the myocardium.

Effect of Triparanol, Nicotinic Acid, and Sodium Dextro-thyroxine on Serum Cholesterol, Triglycerides, and Low-Density Lipoproteins

Hyman Engelberg, Beverly Hills, California

Determination of serum triglycerides and ultracentrifugally separated low-density lipoproteins, in addition to cholesterol, affords a better understanding of the nature of lipid metabolic abnormalities. Accordingly, all 3 parameters were followed in patients who received triparanol, nicotinic acid, or sodium dextro-thyroxine.

Thirty-nine subjects were given triparanol, but the drug was discontinued in 4 individuals because of toxic effects. There was a significant decrease in cholesterol in 16 of the 35 remaining patients and a concomitant reduction of low-density lipoproteins in 6 of the 16. However, in 8 of the 16 who had a drop in cholesterol and in 3 subjects who did not, there was a significant increase in the triglyceride-bearing low-density lipoproteins.

Nicotinic acid was started in 15 patients but continued in only 11 because of severe reaction in 4. In 8 of the 11 subjects, there was a marked reduction of serum cholesterol and the entire low-density lipoprotein spectrum. However, 4 of these 8 individuals stopped the drug because of persistent, mild reactions.

Twenty-eight patients were given sodium dextrothyroxine. It was discontinued in 4 of 9 who had coronary disease because of definitely increased cardiac distress. There was no drop in serum lipids in 7 of the 24 remaining subjects. In the other 17, a significant decrease in cholesterol and in the low-density lipoproteins occurred. Weight loss was noted in 7 individuals, although caloric intake was not reduced.

Angiocardiography in Diagnosis of Transposition of Aorta with Subaortic Ventricular Septal Defect (Origin of Both Great Vessels from Right Ventricle)

Mary Allen Engle and Israel Steinberg, New York, New York

Because of the remarkable streamlining of arterialized blood into the aorta through the ventricular septal defect, which is the only outlet from the left ventricle in this condition, patients with this malformation do not show cyanosis. Their findings are almost indistinguishable from those due to ventricular septal defect with a systemic pressure in the right ventricle and normal origin of the aorta. Diagnosis is important, since repair of the defect when the aorta arises from the right ventricle requires a different approach and use of a hammock-like prosthesis to interrupt the left-to-right shunt and to provide unobstructed blood flow from the left ventricle to aorta. The diagnosis has been accomplished in 7 patients with angiocardiography.

The value of angiocardiography depends on demonstrating the relationship of the 2 great vessels in frontal and lateral projections. In frontal view, in both conditions the pulmonary artery is in its usual position and is unusually convex, while the aorta appears medial to the pulmonary artery and may opacify prematurely or only at the time of left ventricular filling. However, the left lateral or left anterior oblique projection is diagnostic of the abnormal anterior origin of the aorta. When opacified, the transposed aortic valve and arch are seen anterior to the plane of the ventricular septum and above the right ventricle. Angiocardiography is indicated to determine the origin of the aorta in patients with a ventricular septal defect who have a systemic pressure in the right ventricle.

Complete Bypass of the Right Ventricle for the Treatment of Tricuspid Atresia and Related Congenital Cardiac Anomalies

Richard W. Ernst, Arturo Aguillon, David H. Darling, and Eugene N. Nomicos, Dallas, Texas

In tricuspid atresia, superior cava to right pulmonary artery anastomosis will bring about a partial relief of arterial desaturation. Our study concerned itself with the shunting of all caval blood to both lungs with bypass of the right ventricle.

With the animal on total bypass, the superior cava was severed at the right atrium. Through the resulting atrial opening, the tricuspid valve was closed by suture. An end-to-end anastomosis of right pulmonary artery to superior cava was carried out. The proximal right pulmonary artery was ligated. The right atrium was closed. An end-to-side anastomosis of right atrial appendage to main pulmonary artery was carried out, either directly or with interposition of a Teflon graft in cases of short appendage. Thus, the inferior caval blood was shunted into the main pulmonary artery and left lung directly. All animals were kept on heparin for the first 24 hours.

Our longest survivor so far has lived 24 hours. The causes of death were either massive bleeding in a heparinized animal or diminished venous return due to partial occlusion in cases where a wide open lumen was not obtained between the appendage and the main pulmonary artery. We have discontinued the heparin, and by using a graft in cases of short appendage, we have eliminated the compromise of the lumen.

This technic could be applied to achieve total saturation of venous blood in cases of tricuspid atresia and allied lesions.

Cardiovascular Dynamic Responses to Artificial Pacing of Patients in Heart Block (P)

Doris J. W. Escher, John B. Schwedel, Robert Eisenberg, New York, New York, Constantine Gitsios, Salonica, Greece, Nicola Perna, Naples, Italy, and Ahmed Jamshidi, Bridgeport, Connecticut

Twenty-seven patients with heart block and Stokes-Adams seizures have been treated by continuous artificial pacing for periods of from 1 to 24 months via an electrode catheter inserted in the right ventricle through an external jugular vein. The effect of changes in paced rate was studied in 10 of these patients on 11 occasions. Cardiac outputs were determined by dye-dilution curves and the Fick principle, and associated parameters were studied by standard cardiac catheterization technics. Rate increments were 20 to 40 beats/min. Total changes varied from 30 to 112 beats/min. Nine of the 10 patients had low initial cardiac outputs at rest, but only 7 had broadened arteriovenous oxygen differences. Seven of the 10 patients increased their cardiac outputs by 35 to 140 per cent with increase in heart rates. Two of these showed a secondary decrease in output at their highest rates, and 3 were still increasing at the highest rate attempted. Stroke volume was not specifically related to heart rate. Optimal heart rates were highly specific, varying from 60 to 100 beats/min. Central and peripheral blood pressures tended to remain relatively constant, while the total pulmonary and peripheral resistances both changed inversely with the cardiac outputs. The ventilation rate and oxygen consumption tended to be lower with the lowest heart rates. Randomly timed, transmitted atrial beats exerted a marked effect on the central and peripheral blood pressures.

Factors Responsible for the Absence of Metabolic Acidosis and Neurologic Sequelae in a Series of Patients Undergoing Open-Heart Surgery Under Profound Hypothermia with Prolonged Circulatory Arrest

William G. Esmond, Safuh Attar, John Stram, Edward Nygren, Martin Gold, and R. Adams Cowley, Baltimore, Maryland

Open-heart surgery done with continuous circulatory bypass at normothermia, or even with moderate hypothermia of 25 to 30 C., causes a number of problems for the operating surgeon. The continuous flow of blood into the open heart from the lungs and coronary sinus and through insufficient valves obscures vision and lengthens operating time. Continuous open-heart suction hemolyzes red blood cells, causes platelet agglutination and fibrin formation, and introduces room air, containing numerous micro-organisms, directly into the circulating bloodstream. Complete circulatory arrest without extracorporeal circulation under moderate hypothermia at 27 C. solves a number of these problems but limits operating time to 10 minutes and thus allows repair of only simple lesions. Profound hypothermia, in which vital organ temperatures are reduced to 7 to 15 C. and muscle temperature to 22 to 28 C., greatly extends the safe period of circulatory arrest to as long as 40 to 60 minutes, since metabolism at a mean core temperature of 10 C. is reduced to one-tenth to one-sixteenth of metabolism at normal temperature.

Extracorporeal circulation with a pump-oxygenator combined with an efficient blood heat exchange system allows a reduction in temperatures of vital organs to 10 to 15 C. to be accomplished within 22 minutes. A study of the thermokinetics of heat transfer has indicated that heat can be transferred from vital tissues only by maintaining a sufficiently high flow rate of cold blood for a

long enough period of time to effect the necessary transfer of thermal energy. The temperature drop of the blood in 1 passage through the heat exchanger is dependent on blood and cooling water flow rates and temperatures and can be expressed in exact terms for all heat exchangers. The use of the most efficient blood heat exchangers available, however, will not reduce the temperature of vital organs effectively unless high flow rates are maintained which will sustain mean blood pressure sufficient to proportion blood to tissues adequately.

Flow rates adequate to sustain metabolism at normothermic levels were employed for the induction and recovery from profound hypothermia in a consecutive series of 10 patients undergoing open-heart surgery for the repair of congenital heart defects. No postoperative acidosis and no neurologic sequelae resulted. It is believed that factors responsible for this result were (1) an efficient blood heat exchange system which allowed rapid induction of profound hypothermia and effective rewarming; (2) high flow rates resulting in effective vital organ cooling; (3) the high tissue tension of oxygen produced by the efficient disc oxygenator used, which provided stores of readily available oxygen during the intial period of circulatory arrest; (4) maintenance of pH at 7.4 at 10 C. by employing a gas mixture of 5 per cent CO_2 and 95 per cent O_2 in the oxygenator during cooling; this allows a greater quantity of oxygen to dissociate from hemoglobin at a given oxygen tension than could occur if pH were allowed to rise during cooling.

Pathologic-Radiologic Correlative Study of Coronary Artery Disease (P)

Joseph H. Eusterman, Richard W. P. Achor, Owings W. Kincaid, and Arnold L. Brown, Jr., Rochester, Minnesota

The increasing use of coronary arteriography in selecting patients for direct surgical procedures on the coronary arteries prompted a study to determine whether roentgenographic visualization accurately indicates existing coronary disease. The coronary arteries of 50 hearts obtained at necropsy were injected with 85 per cent solution methylglucamine diatrizoate, and appropriate roentgenograms were made. Detailed sectioning and anatomic examination of the arteries were then carried out. The arteries of each heart were arbitrarily divided into 16 segments, and the degree and character of luminal stenosis or occlusion in each segment were estimated from the arteriograms. These findings were then compared with the anatomic findings.

In a total of 479 segments, diffuse arterial disease (stenosis or occlusion greater than 5 mm. in length) was graded similarly in 291 segments (61 per cent) by both arteriography and anatomic examination. Actual involvement was underestimated by arteriography in 107 segments (22 per cent) and overestimated in 81 (17 per cent). Focal arterial lesions (stenosis or occlusion less than 5 mm. in length) were present in 89 of the 479 segments. Ten (11 per cent) of these were graded correctly from arteriograms, 76 (85 per cent) were underestimated, and only 3 segments (4 per cent) were overestimated as to the degree of disease present. Arteriographic estimation of the degree of disease present seemed least reliable in the proximal arterial segments, which are the regions considered most amenable to direct surgical attack. The results of this study suggest that more experience from correlative studies is necessary before too much reliance is placed on interpretation of coronary arteriograms.

Estimation of Coronary and Bronchial Blood Flow by Isotope-Dilution Technic

John R. Evans and Lloyd T. Iseri, Downey, California

Examination of numerous brachial artery isotope-dilution curves frequently revealed 1 or 2 separate "humps" on the descending slope. Simultaneous precordial and brachial artery dilution curves were obtained in order to identify the humps as being due to (1) bronchial artery and (2) coronary artery recirculations. By increasing the sensitivity of counting system and by increasing the concentration of isotope in the injected bolus, the percentage of measurable curves was greatly increased. On the assumption that recirculation of blood containing the isotope was similar to a second injection into the main stream and that the fraction of isotope entering the bronchial and coronary circulations was proportionate to their flow rate, a formula was derived to quantitate the respective rate of flow. A model which incorporated a "right and left ventricle," a "coronary artery," the "myocardial bed," and a "brachial artery" was set up to test the formula. Satisfactory agreement was found between actual and calculated flows.

Coronary flow calculated in 9 control patients ranged from 315 to 779 ml. per minute and 4.30 to 7.78 per cent of the cardiac output. Bronchial flow ranged from 5.3 to 9.9 per cent of cardiac output. Coronary blood flow in 9 cases of coronary disease ranged from 86 to 283 ml. per minute and 2.5 to 4.8 per cent of cardiac output. The precordial counting method did not prove feasible.

It is concluded that brachial artery isotope-dilution technic may be adaptable to the estimation of coronary and bronchial circulations.

Increased Shunt Tolerance Provided by Experimental Production of Biventricular Hypertrophy

Richard H. Evans, Howard L. Bresler,† James A. Lennertz, Robert W. Harrison, and Peter V. Moulder, Chicago, Illinois

Attempts to create a high flow through the entire pulmonary vascular bed in an effort to study its chronic effect usually fail, with development of a fatal pulmonary edema in the immediate postoperative period. Hypertrophy of the right or both ventricles has been induced with a preliminary, reversible coarctation of the pulmonary artery (and aorta) prior to creation of a large shunt.

Three groups of animals were studied. Systemic-pulmonary artery shunts were created in 20 dogs, utilizing a Teflon graft of 6.4 mm. I.D. from the subclavian artery to the left pulmonary artery. Ten died within 3 to 4 hours postoperatively; all were dead within 4 days. In 15 dogs, the main pulmonary artery was constricted with a 1.5-cm. Teflon band. One month later, the band was removed, and a similar systemic-pulmonary artery shunt was created. Four survived from 1 to 5 days; all eventually died of pulmonary edema. The right ventricular wall thickness was 5 to 9 mm. (normal about 2 to 4 mm.). Eleven dogs were subjected to banding of the pulmonary artery and descending thoracic aorta. After 3 to 4 weeks, the bands were removed and a similar shunt introduced. To date, 7 of 11 aninmals have survived from 3 weeks to 2 months. Cardiac catheterization in 2 animals at 1 month has indicated patency of the shunt with a calculated flow of 2 to 2.5 L./min. The animals which did not survive showed marked biventricular hypertrophy.

Effect of Medical Treatment on Prognosis in Severe Hypertension

Richard G. Farmer, Ray W. Gifford, Jr., and Edgar A. Hines, Jr., Rochester, Minnesota

Follow-up information was obtained on 161 patients for whom antihypertensive treatment was initiated at the Mayo Clinic between 1951 and 1954. Ninety-seven had retinal changes of group III hypertension and 64 of group IV (Keith-Wagener).

Thirty (31 per cent) of the patients with group III hypertension were alive after an average of 6.5 years. The average interval from starting treatment to death of 67 patients was 2.5 years; the most frequent cause of death was cerebral vascular accident.

Seventeen (27 per cent) of the patients with group IV hypertension were alive after an average of 6.7 years. The average interval from starting treatment to death of 47 patients was 1.7. years. Cerebral vascular accident and renal failure were the most frequent causes of death.

Increase of blood urea, recent onset of hypertension, marked albuminuria, and pretreatment diastolic pressure above 120 mm. Hg were bad omens. Age at onset, sex, electrocardiographic abnormalities, and history of cerebral vascular disease did not affect prognosis.

About three-fourths of the patients received ganglion-blocking agents, alone or in combination, but these patients did not fare better than the others. All 9 patients who stopped treatment died. Forty-four of 47 living patients and 71 of 114 patients who eventually died had continued treatment until time of follow-up or of death. For 3 living patients and 34 dead patients, follow-up information about medication could not be obtained.

Blood Flow in the Descending Canine Thoracic Aorta

Walter Feder and Emmet B. Bay, Chicago, Illinois

Instantaneous blood flow velocity in the intact descending thoracic aorta in 15 anesthetized dogs was measured in a wide variety of conditions. The DC electromagnetic flowmeter was employed with "nonpolarizable" Ag AgCl electrodes, which were shown to be steady under various types of electrical and mechanical stress. The accuracy of the measurements in the dog was established in the following ways: (1) In the case of zero flow, the average instrument "drift" was demonstrated to approximately 1 cc./sec, compared to mean flow velocity in the order of 25 cc./sec.; (2) volume flow was calculated from the area under pulsatile velocity flow curves during a known time interval and compared with the measured volume; and (3) after sacrifice of the animals in 8 instances, steady flow measurements made by running blood through the aorta were compared with the collected volume. Accurate and reproducible values with about 5 per cent error were obtained.

The effect of changes in heart rate and rhythm on the nature of the velocity flow curve were analyzed. Observations were made on the effect of premature atrial and ventricular contractions, idioventricular beats, and other arrhythmias on the velocity flow curve. The effect of epinephrine on the rate and duration of flow was studied. Back flow was noted as the abdominal aorta was approached.

Active and Passive Changes in Pulmonary Blood Volume (P)

James W. Feeley, T. David Lee, and William R. Milnor, Jr., Baltimore, Maryland

To learn whether shifts in distribution of blood between pulmonic and systemic circuits are entirely passive, i.e., attributable to changes in vascular transmural pressure rather than changes in vessel distensibility, the effects of various drugs that alter pulmonary hemodynamics were studied in anesthetized dogs (42 animals, 64 experiments). Changes in volume, pressures, and flow in the pulmonary vascular bed were measured, using an indicator-dilution method with consecutive injections into pulmonary artery and left atrium to determine pulmonary blood volume (PBV).

Mean control PBV was 107 ml./10 Kg. (S.E.M. ± 2 ml.). Constant intravenous infusion of epinephrine or norepinephrine (0.5 to 2.0 μg./Kg./min.) increased PBV (+ 26 ml. and + 59 ml./10 Kg., respectively), but this increase was proportional to a simultaneous increase in effective pressure in pulmonary artery [P(pa)] and left atrium [P(la)] and was, therefore, predominantly passive. Intrapleural pressure did not change significantly. Isoproterenol (2 μg./Kg./min.), in contrast, increased PBV (+ 23 ml./10 Kg.) but decreased P(pa) and P(la), implying active increase in pulmonary vascular distensibility. Intravenous serotonin (0.65 mg./Kg./min.) or histamine (5μg./Kg./min.) actively decreased distensibility. There was no consistent relation between changes in systemic pressure and resistance and pulmonary vascular responses. These results show that both active and passive mechanisms can alter PBV in the intact animal.

With each of the agents tested, changes in PBV were accompanied by inverse changes in pulmonary vascular resistance, suggesting that the caliber of the larger pulmonary vessels (which predominantly influence PBV) and of the smaller vessels (which influence resistance) varied in the same direction.

Experimental Reactivation of Subsiding Rheumatic Fever (P)

Alvan R. Feinstein and Mario Spagnuolo, Irvington-on-Hudson, New York

The present work demonstrates the experimental provocation of rheumatic activity in asymptomatic patients and provides an explanation for the mechanism of the post-therapeutic rebound phenomenon in rheumatic fever.

A 2-week course of treatment with prednisone, aspirin, or nothing was given experimentally to 88 randomly allocated patients convalescing from rheumatic fever. The experimental treatment in each patient was begun exactly 1 month after discontinuation of the initial course of treatment, a time when all patients had no clinical evidence of rheumatic activity. During retreatment, the sedimentation rate and C-reactive protein were invariably lowered by prednisone but were sometimes raised by aspirin. The mean hematocrit rose with prednisone and fell with aspirin.

When the experimental therapy was stopped, a recrudescence of either fever, tachycardia, arthralgia, erythema marginatum, or congestive heart failure occurred in 9 of 29 patients treated with prednisone and in 1 of 29 patients treated with aspirin. The 30 controls remained asymptomatic. The experimental rebounds were more frequent in patients with severe cardiac damage and occurred only in patients who had shown clinical or laboratory evidence of rheumatic activity immediately after their initial course of treatment.

These results contradict the hypotheses that the rheumatic rebound is due either to (1) polycyclic rheumatic activity, (2) relative hypoadrenalism, or (3) insufficient duration of therapy. They indicate that the rebound represents the appearance of rheumatic inflammation which accumulated under therapeutic suppression. They also indicate that anti-inflammatory therapy can be detrimental in asymptomatic rheumatic patients whose only abnormalities are in laboratory tests.

Cardiac Sequelae of Acute Rheumatic Fever: A Seven-Year Follow-Up of 447 Patients

Alvan R. Feinstein, Irvington-on-Hudson, New York, Harrison F. Wood, Wallingford, Connecticut, Angelo Taranta,† Esther Tursky, and Mario Spagnuolo, Irvington-on-Hudson, New York

The present study reports the cardiac sequelae of rheumatic fever in 447 children and adolescents receiving continuous antistreptococcal prophylaxis and examined objectively at monthly or bimonthly intervals for an average of 7.2 years.

On the basis of the events of the acute attack, the patients could be divided into 5 categories, each of which had a different incidence of future heart disease: (1) Seventy-seven patients, when first seen, had had more than 1 attack of carditis; 6 of these are now dead, and 62 have residual heart damage.

One hundred and ninety patients were in their first attack of carditis: (2) Of 38 who had congestive failure or at least moderate cardiomegaly during the acute attack, 2 are now dead, and 30 have residual heart damage. (3) In 98 patients, the most severe manifestation of carditis was basal or apical diastolic murmur (with or without systolic murmur); 1 of these is now dead, and 46 have residual heart damage. (4) In 54 patients, the most severe manifestation of carditis was an organic apical systolic murmur; 12 of these have rheumatic heart disease, and none has died.

(5) No heart damage has developed in the 180 patients who were free of carditis during the acute attack.

Despite prophylaxis, the patients developed 48 recurrences of rheumatic fever during the period of observation. In the recurrent attacks, carditis did not appear in patients who were previously free of it. In patients who had had carditis, the recurrences often, but not always, made the heart worse.

These results indicate that patients with rheumatic fever form at least 5 different groups, each with a different cardiac prognosis, depending on the state of the heart during the acute attack. Heart disease does not appear to develop in patients who were free of carditis initially. Its persistence is most likely in patients with diastolic murmurs, and its severity is greatest in those with cardiomegaly or decompensation during the acute attack.

Pattern of Symptoms, Pretreatment Interval, and the Prognosis of Acute Rheumatic Fever

Alvan R. Feinstein and Juanita G. Zagala, Irvington-on-Hudson, New York

Rheumatic fever reportedly leaves less residual heart disease if anti-inflammatory treatment is begun soon after onset of symptoms. Using the rigorous Jones criteria for carditis, the present study has examined this concept by correlating the severity of the arthropathic presenting features, the pretreatment interval, the incidence of carditis on admission, and the incidence of residual heart disease in 247 consecutive children and adolescents with acute rheumatic fever. The data are tabulated below:

Incidence of carditis on admission/total number of patients in each category

Severity of presenting joint features	Pretreatment interval: First attacks 0-2 wks.	First attacks > 2 wks.	Recurrent attacks 0-2 wks.	Recurrent attacks > 2 wks.
Arthritis	30/110	10/20	22/39	6/7
Arthralgia	4/8	7/8	7/7	1/1
No joint symptoms	11/13	16/16	10/12	5/6

Incidence of residual heart disease/total number of patients with carditis

Severity of presenting joint features	Pretreatment interval: First attacks 0-2 wks.	First attacks > 2 wks.	Recurrent attacks 0-2 wks.	Recurrent attacks > 2 wks.
Arthritis	24/30	8/10	19/22	6/6
Arthralgia	3/4	7/7	7/7	1/1
No joint symptoms	9/11	16/16	8/10	5/5

The results show that established carditis is usually not eradicated by treatment and that the incidence of residual heart disease is *not* significantly lower ($x^2 = 2.0$, $p > 0.1$) with early treatment. The data indicate that the benign total cardiac results of early treatment are often due not to therapy but to the absence of carditis in patients whose severe arthritis brings them to treatment quickly. Recurrent attacks are more frequent in patients with established heart disease, and they come to treatment earlier than those with first attacks.

The data indicate that rheumatic fever, clinically as well as pathologically, is more likely to bite the heart when it spares or merely licks the joints. However, when it bites the joints, it is more likely to lick or spare the heart.

Calcific Constrictive Pericarditis with Secondary Hypoprothrombinemia, Thrombocytopenia, and Hemorrhage

Egbert H. Fell, Irving A. Friedman, George W. Stuppy, Milton Weinberg, Zwi Steiger, and Takashi Iwa, Chicago, Illinois

During the past 6 years we have studied and treated 9 patients with calcific constrictive pericarditis. Three of the 9 were women; each had had known heart disease for from 2 to 6 years. All had moderate to severe upper gastrointestinal hemorrhages, 2 had severe hypoprothrombinemia (25 to 30 per cent), and the third had a thrombocytopenia (25,000 platelets). All had markedly increased venous pressures, ascites, and enlarged livers and spleens.

Calcific constrictive pericarditis, according to the literature and in our experience, occurs more commonly in the male, and anemia secondary to gastrointestinal bleeding is a rare complication. Hypersplenism appeared to be secondary to the passive congestion.

These women presented serious hemorrhagic problems, and successful results were obtained in all 3 patients with the use of fresh blood, fresh platelet packs, and fresh frozen plasma before, during, and after pericardiectomy.

Congenital Malformations of the Lung and Their Circulatory Significance

Charlotte Ferencz, Buffalo, New York

This report calls attention to the occurrence of congenital circulatory disturbances resulting from the malformations of the lung.

The embryonic lung is derived from the primitive foregut and shares the vascular channels of the dorsal aortae and the cardinal venous plexus, while the fully developed organ has independent arterial and venous connections with the heart. This transition from the systemic to the pulmonary circulation is an essential feature of pulmonary development. Developmental disturbances result in 3 major types of vascular anomalies, which are present singly or in combination: (1) persistent

systemic arterial supply, (2) small or absent pulmonary artery, (3) persistent venous drainage into derivatives of the cardinal venous system.

Anomalous branches of the descending aorta frequently supply malformed bronchopulmonary segments and complicate their surgical treatment. Hemoptysis may occur. Hypoplasia of a main branch of the pulmonary artery may or may not be associated with obvious hypoplasia of the lung. Most patients are asymptomatic and show normal cardiopulmonary function. The occurrence of pulmonary hypertension in the developmentally normal left lung of an infant with hypoplasia of the right lung is documented by hemodynamic and necropsy studies. In patients with persistent systemic venous drainage of the lung, the hemodynamic consequences of the malformation appear to vary widely. A correlation of hemodynamic and respiratory function studies permits an accurate physiologic determination of the anatomic arrangement in most instances. Complementary methods of investigation include cardiac catheterization, selective angiocardiography, and determination of the oxygen uptake of each lung.

Pulmonary Edema as an Initial Manifestation of Myocardial Infarction

Matthew J. Ferguson, New York, New York

Pulmonary edema is an extremely rare initial symptom of acute myocardial infarction. A total of 450 consecutive patients with myocardial infarction admitted to the St. Vincent's Hospital of the City of New York were studied. The first 150 patients were studied retrospectively, and the remaining patients were observed directly for the occurrence of pulmonary edema as the initial manifestation of myocardial infarction.

To date, not 1 case of acute myocardial infarction with the initial symptom of pulmonary edema has been documented.

There has been a small group of 12 patients who were admitted with pulmonary edema and myocardial infarction. However, when these cases were analyzed, they were found to be either elderly patients with long histories of cardiac disease and previous failure or, more commonly, active people who had chest pain and other acute symptoms 3 to 7 days prior to admission.

This latter group usually continued their routine activities until pulmonary edema forced them to seek medical attention. All of these patients died within hours, and autopsies revealed infarctions obviously dating days before their admission.

Another group of 15 patients who presented with acute chest pain and severe dyspnea died suddenly without evidence of pulmonary edema. Postmortems in these patients showed coronary occlusion. (Infarction had not yet had time to develop.) Deaths were attributed to cardiac standstill or arrhythmia.

Effect of Therapy of Unsuspected Pyelonephritis on Fetal Mortality and Prematurity

Frank A. Finnerty, Jr., Gloria DeCarlo Massaro, and Nikos Kakaviatos, Washington, D. C.*

Bacteriologic studies were performed on the urine of 202 *asymptomatic* pregnant patients. A total of 102 (toxemia-suspect patients) showed only albuminuria, whereas 100 patients were entirely normal. The urine of 25 of the 102 patients with albuminuria grew pathogenic organisms with colony counts of more than 100,000 bacteria per ml. There was a positive gram stain on the unspun urine in 24 of the 25 patients.

The urine of 14 of the normal patients grew pathogenic organisms with colony counts of more than 100,000 bacteria per ml. A positive gram stain was noted in each of the 14 patients.

Antibiotic therapy was withheld from 12 of the toxemia-suspect patients and from 7 of the "normal" patients whose urine showed significant colony counts and positive gram stain. None of these patients developed clinical signs and symptoms of pyelonephritis. In the treated group, there was no fetal mortality, but there was evidence of prematurity in 1 infant. In the untreated group, there was 1 instance of fetal mortality and evidence of prematurity in 4 infants.

These data suggest that a careful search for and treatment of unsuspected genitourinary infection in all pregnant patients not only might prevent the development of chronic pyelonephritis, but also would significantly reduce the incidence of fetal mortality and prematurity.

Observations on the Hemodynamics of Sustained Pulsus Alternans Induced by Myocardial Cooling

Walter L. Floyd, Marcus L. Dillon, and John W. Reeves, Durham, North Carolina

Hypothermia produces profound prolongation of myocardial relaxation and impaired ventricular filling due to extension of relaxation far into the period of ventricular inflow. During the period of altered myocardial relaxation between 23 and 32 C., sustained pulsus alternans occurs spontaneously or can be induced by artificial elevation of heart rate. Rewarming the heart to normal invariably results in disappearance of pulsus alternans.

The simultaneous measurement of phasic proximal aortic flow by means of an electromagnetic flowmeter, central aortic pressure, left interventricular pressure, and left atrial pressure allowed detailed observations on pulsus alternans in 14

hypothermic dogs. In an alternans couple, incomplete relaxation prior to the small or ineffective beat resulted in an elevated end-diastolic pressure and reduced ventricular filling time. By contrast, end-diastolic pressure was low, and filling time increased prior to the normal beat.

Sustained alternans could be obliterated by selectively elevating left atrial pressure or reducing aortic pressure. Similarly, alternans could be induced by lowering left atrial pressure or elevating aortic pressure. Disappearance of alternans was noted without change in atrial or aortic pressure when spontaneous slowing of heart rate occurred.

The mechanism of pulsus alternans is a complex one involving heart rate, outflow resistance, and atrial filling pressure, but under the conditions studied, it is felt that at physiologic heart rates, an abnormality in myocardial relaxation is a prerequisite to its occurrence and that the observed changes in the character of contraction are explained on the basis of altered ventricular filling rather than alternate deletion of contractile elements within the myocardium.

Clinical Technic for Determining the Fraction of Left Ventricular End-Diastolic Volume Ejected per Beat (P)

Roland Folse, Eugene Braunwald, and Maurice M. Aygen, Bethesda, Maryland

A technic has been developed for determining the fraction of left ventricular end-diastolic volume which is ejected during each cardiac cycle. Radioiodinated diodrast is rapidly injected into the left ventricle, and the fraction of isotope which is discharged from this chamber per beat is determined with a scintillation probe placed on the chest wall over the left ventricle. Left ventricular end-diastolic volume may be estimated from the stroke volume, determined by the dye-dilution method and the fraction of isotope discharged per beat. Difficulties resulting from inadequate mixing of isotope in the left ventricle are minimized by this technic, since the probe detects indicator in the entire left ventricular cavity. The accuracy of this technic was first demonstrated in a circulatory model and then in open-chest dogs, in which ventricular dimensions were continuously monitored by means of mercury-in-rubber gauges. In 20 patients without detectable abnormalities of left ventricular function, the fraction of left ventricular volume discharged averaged 38 ± 8 per cent per beat, and the end-diastolic volumes averaged 90 ± 26 ml./M.^{2}/BSA. In 20 patients with heart failure and/or valvular regurgitation, in whom left ventricular function was compromised, the fraction of left ventricular volume discharged into the aorta averaged 16 ± 5 per cent per beat, and the end-diastolic volumes averaged 204 ± 76 ml./M.^{2}/BSA. This technic has been found to be sensitive to changes in left ventricular function and is practical to apply routinely in the course of left heart catheterization.

Surgical Treatment of Complete Heart Block

William B. Ford, Robert S. Cartwright, and James W. Giacobine, Pittsburgh, Pennsylvania

Development of the bipolar myocardial electrode and transistorized pacemakers has permitted long-term alleviation of symptoms in patients with Stokes-Adams seizures due to complete heart block. Surgical therapy is instituted in patients with frequent attacks when the effects of the block cannot be controlled by drugs. A small anterior thoracotomy incision permits suture of the electrode to the ventricular myocardium. In a group of 16 patients treated in this manner, the conducting wire was passed through the chest wall to a small, externally placed transistorized unit in 11, while an implanted subcutaneous pacemaker was utilized in 5. There was virtual elimination of symptoms in all patients. However, 3 patients in the first group have subsequently died, 1 due to wire breakage, 1 due to latent infection with extrusion of the electrode, and 1 due to incidental renal failure. Internal wire breakage has occurred in 2 additional patients, reoperation being required in 1. The danger of infection appears less with the implanted pacemaker, and recent modifications of the electrode wires have reduced the likelihood of wire breakage. Overall results of the procedure are sufficiently favorable to recommend continued exploration of this form of treatment.

Cardiovascular Response to Exercise in Patients with Angina Pectoris

Glenn L. Foster and Thomas J. Reeves, Birmingham, Alabama

By means of percutaneous brachial artery puncture and retrograde aortic catheterization, hemodynamic studies were performed on 16 patients from 36 to 56 years old with angina pectoris without congestive failure. Eleven healthy males from 21 to 51 years old were also studied. At rest and during graded levels of supine leg exercise (the maximum being sufficient approximately to triple the basal oxygen consumption in the patients and increase it 4 to 5-fold in the normals), the oxygen consumption, cardiac output (dye dilution), central aortic pressure, and the first time derivative of the aortic pressure were recorded. From these data, the mean ejection flow, maximum rate of pressure rise, and stroke power were calculated.

For the same level of oxygen consumption during exercise without chest pain, the patients had

a lower cardiac output, stroke volume, and mean ejection flow when compared to the normal subjects. (For example, at 450 cc./min./M.^{2} oxygen consumption, the cardiac output of the normals was within Donald's limits for normal and averaged 6 L./min./M.^{2}, while the patients averaged 4.3 L./min./M.^{2}. The stroke volume of the normals averaged 55 cc./M.^{2}, whereas the patients averaged 42 cc./M.^{2}, and the mean ejection flow for normals averaged 205 cc./sec./M.^{2}, while in patients it averaged 155 cc./sec./M.^{2}.)

In 4 patients who developed chest pain during exercise, the mean ejection pressure remained unchanged, while the maximum rate of aortic pressure rise (MRPR) fell abruptly, returning to previous levels as pain disappeared. The MRPR in normals and patients without chest pain showed no discontinuity.

Studies in the Prevention of Toxic Reactions Incident to Contrast Angiography (P)

John H. Foster, Robert T. Sessions, Duncan A. Killen, and Harold A. Collins, Nashville, Tennessee

Progress in cardiovascular surgery in the past decade has been accompanied by increasing application and usefulness of contrast angiography. Toxic reactions incident to arteriographic procedures have assumed greater importance. Previous studies from this laboratory have quantitated the toxic properties of the various contrast media. The present study compares the effectiveness of 2 substances, 20 per cent glucose and low molecular weight dextran, in preventing the toxic responses to intravascular injection of contrast agents.

The azotemia and paraplegia produced by intra-aortic injection of sodium acetrizoate (Urokon 70 per cent) and the lethal effect of large intravenous doses (4 cc./Kg.) of the same agent were observed in mongrel dogs with and without premedication with standardized doses of 20 per cent glucose and low molecular weight dextran. When the intravascular injection of sodium acetrizoate is preceded by an injection of 20 per cent glucose or low molecular weight dextran, the incidence of the toxic responses can be markedly reduced. The apparent mechanism of this protective effect seems to be different for the 2 substances involved. Clinical application of the prophylactic use of these protective substances in angiography seems warranted.

Clinicopathologic Study of Patients with and without Angina Pectoris Preceding Initial Myocardial Infarction

Robert L. Francis, Richard W. P. Achor, and Arnold L. Brown, Jr., Rochester, Minnesota

Case records of patients from Rochester, Minnesota, who had been given a clinical diagnosis of initial acute myocardial infarction and who died and came to necropsy in the years 1935 through 1956 were reviewed. In 72 (48 per cent) of the 150 cases, angina pectoris was present for more than 1 month prior to the first diagnosed infarction, and in 78 (52 per cent) there was no antecedent angina. Sex distribution was identical in both groups, but the mean age was 2.3 years less for the patients with angina. Death occurred during the first month after the initial infarction in 30 (42 per cent) of the 72 patients with prior angina and in 17 (22 per cent) of the 78 without this symptom. The mean duration of life from initial infarction until death was 36.8 months for the patients without angina and 15.9 months for those with angina. For this latter group, the mean time from onset of angina pectoris until infarction was 22.4 months. Diabetes mellitus, hypertension, obesity, and congestive heart failure occurred more frequently in the group with angina. Acute myocardial infarction, initial or recurrent, was the cause of death in 47 (65 per cent) of the patients with prior angina and in 30 (38 per cent) of those without prior angina.

It is concluded that patients with antecedent angina pectoris who sustain an initial acute myocardial infarction have poorer immediate and long-term survival rates and greater disability than do patients without such a history.

Acute Pulmonary Edema of High Altitude (P)

Herbert L. Fred, Alexander M. Schmidt, Salt Lake City, Utah, Talcott Bates, Monterey, California, and Hans H. Hecht, Salt Lake City, Utah

Two normal athletic subjects, residing at sea level, developed rapidly progressing illness characterized by intense dyspnea after 2 days of skiing at Alta, Utah (8,600 to 11,500 feet, 2,600-3,750 M.). Almost moribund, they were hospitalized in Salt Lake City (4,500 ft., 1,372 M.). Both recovered on bed rest and oxygen therapy. Each had clinical and radiologic findings of severe pulmonary edema without significant cardiac enlargement. On admission, an accentuated second pulmonic sound was present in patient L.R.B.; an accentuated, split P_2 with a presystolic gallop was noted in patient T.B. Serial electrocardiograms and hematologic studies were normal. An extensive search for bacterial, viral, or fungal infection was negative. Patient T.B. underwent cardiac catheterization on the second day of hospitalization. There was arterial desaturation not fully corrected by oxygen therapy, moderate elevation of PA pressure (67/40 mm. Hg), and a marked increase in pulmonary vascular resistance (12.4 mm. Hg/

L./M.^{2}). Valid "wedge" pressure could not be recorded despite adequate positioning. Left atrial pressure, however, was normal (10 mm. Hg). Right ventricular end-diastolic and right atrial pressures were elevated (9 mm. Hg). Spirometry was normal on recovery.

This syndrome represents a pulmonary vascular phenomenon with constriction, presumably on the venous side of the pulmonary circulation. Right ventricular overload may occur. The obvious dependence of the illness on altitude suggests that lowered oxygen tension is the major causative factor. Pulmonary edema occurs when a high flow rate (exercise) through the pulmonary vascular bed is met by distal (venous) obstruction. This disorder may be considered another example of the relation between reduced oxygen tension and pulmonary vascular reactivity.

Effect of Arrhythmias and Stress on the Function of Semilunar and Atrioventricular Valves

Ben Friedman, Dallas, Texas

The holding function of the valves of the dog's heart was tested in response to arrhythmias and a variety of stress. The presence of regurgitation was tested by insertion of a sensitive thermistor device in the chamber upstream to the valve and the injection of cold Ringer's solution into the downstream chamber. A sharp decline in temperature within 1 or 2 heartbeats following injection signaled the presence of valvular insufficiency.

Regurgitation was demonstrated in the tricuspid and mitral valves consistently with ventricular arrhythmias, at times during auricular fibrillation, but not with auricular tachycardias unless ventricular muscle function was impaired.

Regurgitation across the semilunar valves was not effected by any arrhythmias except ventricular flutter and fibrillation.

Hypervolemia, hypoxia, and hypertension did not result in regurgitation across the semilunar valves except under extreme conditions of deterioration of ventricular muscle function. The tricuspid and mitral valves could be made insufficient by lesser degrees of stress.

Congestive heart failure may frequently be aggravated or precipitated by the appearance of ectopic rhythm or by hemodynamic stresses. The observations here recorded suggest that one of the mechanisms may be the added myocardial work load due to regurgitation across anatomically normal atrioventricular valves induced by arrhythmias and myocardial dilatation.

Vascular Connections Established by Implanting Arteries into the Lower Extremity Using Plastic Sponge as an Intermediary (P)

Edward W. Friedman and Peter B. Lambert, Boston, Massachusetts

This report describes the use of plastic sponge in establishing functional connections between a transplanted artery and the vascular bed of the lower extremity.

In preliminary studies in rats and rabbits, poly vinyl alcohol sponge was placed around the femoral vessels which were ligated distal to the sponge. Microangiograms revealed filling of vessels in the interstices of the sponge with x-ray contrast medium injected via the femoral artery. In addition, vascularization of cubes of polyvinyl alcohol sponge implanted in the rabbit ear was demonstrated in serial stereomicroangiograms.

In rabbits, a cube of polyvinyl alcohol sponge was placed around the superficial epigastric vessels which were ligated distal to the sponge. One to 5 weeks later, the sponge was transferred to a pocket in the muscles of the lower thigh, retaining the epigastric vessels as a pedicle, and the femoral artery was ligated at several points distal to the epigastric vessels. Two to 12 weeks later, the epigastric artery was cannulated for in vivo angiographic and postmortem microangiographic study. In all animals, the epigastric artery pulsated vigorously and was considerably dilated. Nonpulsatile backflow from the distal cut end of the artery at a pressure of 40 mm. Hg suggested connections with a rich collateral vascular bed. The angiograms showed contrast medium to have filled vessels in the sponge and arteries and veins of the thigh, leg, and, in one animal, the foot. Best filling of the vessels of the limb was obtained 6 or more weeks after transplantation of the sponge.

Comparison of the Local Effects of Nitroglycerin, Sodium Nitrite, Papaverine, and Atropine on Coronary Vascular Resistance

Edward D. Frohlich and Jerry B. Scott, Fort Knox, Kentucky

Although many studies have reported that the above agents dilate coronary arteries, none allows comparison of steady state effects over concentration ranges which might occur during therapy. Therefore, isotonic solutions containing nitroglycerin (0.1 mg./ml.), sodium nitrite (7.25 mg. nitrite/ml.), papaverine hydrochloride (1.47 mg. papaverine/ml.), and atropine sulfate (1.70 mg. atropine/ml.) were infused into the coronary vascular bed of 18 beating dog hearts perfused with arterial blood at a constant rate (average 92 ml./min.). Perfusion pressure decreased as a function of the infusion rate of nitroglycerin, sodium nitrite, and papaverine hydrochloride over the range of zero to 2.6 ml./min. and was not changed by atropine sulfate and isotonic sodium chloride. Resistance decreased 20 per cent at an infusion rate which provided 0.12 mg. nitroglycerin, 8.70 mg. nitrite, and 0.74 mg. papaverine.

By using the formula (QT interval × heart rate)/60 to obtain an index of the proportion of a minute spent by the ventricle in systole and, hence, of coronary vessel transmural pressure, it was determined that the pressure changes resulted from active dilation. The fact that atropine increased the proportion of a minute spent in systole without changing pressure suggests that atropine may also produce some dilation.

These findings indicate that nitroglycerin, nitrite, and papaverine produce active coronary artery dilation when administered locally. The relative potencies, on the basis of weight of the active ion, indicate that nitroglycerin is approximately 70 times more active than the inorganic nitrite and approximately 6 times more active than papaverine.

Prevention and Treatment of CO_2 Intoxication During Oxygen Inhalation in Pulmonary Emphysema by Aminophylline Alone and Together with Acetazoleamide

Morton Galdston and Martin B. Myles, New York, New York

Aminophylline enhances the respiratory response of normals to inhaled CO_2. Studies in this laboratory demonstrated that it also enhances the depressed respiratory response of emphysema patients to inhaled CO_2 and that acetazoleamide intensifies this response. The present studies illustrate the value of aminophylline in prevention and treatment of CO_2 intoxication during oxygen inhalation in a patient with emphysema and cor pulmonale during heart failure and following recovery. Aminophylline (0.5 Gm., 6.9 mg./Kg.) was administered intravenously followed by a sustaining infusion of 100 mg./hour over 2½ to 3½ hours. Comparisons were made between minute ventilation, arterial pCO_2, and pH in room air and during the first 12 and last 4 minutes of 2 to 4 one-hour oxygen periods with intervening half-hour room air periods. In 3 studies in heart failure, respiratory depression (13 to 27 per cent, from 6.9 to 7.8 to 5.7 to 6.0 L./min.), arterial pCO_2 retention (from 72 to 75 to 85 to 100 mm. Hg), and pH depression (from 7.35 to 7.37 to 7.22 to 7.30) occurred during the first 12 minutes in oxygen. Aminophylline administration begun thereafter (2 studies) stimulated respiration and restored control pCO_2 and pH levels. Resumption of oxygen following room air now caused only slight respiratory depression without CO_2 retention or pH depression. Glucose administered in place of aminophylline had no beneficial effect. As heart failure was compensated partially by digoxin and completely by digoxin with acetazoleamide, hypercarbia and oxygen-induced respiratory depression and CO_2 retention became less intense. Acetazoleamide enhanced the respiratory-stimulating action of aminophylline sufficiently to compensate for the metabolic acidosis induced by acetazoleamide.

Overaeration of the Left Lung as a Manifestation of Patent Ductus Arteriosus

Joseph M. Garfunkel and John A. Kirkpatrick, Jr., Philadelphia, Pennsylvania

Overaeration of the left lung, associated with diminution of the vasculature within the left lung as compared with the right, has been seen in 3 patients with patent ductus arteriosus. The first was a 3-month-old infant who presented with progressive respiratory distress, cardiac enlargement, and a systolic murmur. Thoracotomy was undertaken to explore for an obstructive lesion of the left pulmonary artery. The only anomaly found was a large patent ductus arteriosus, ligation of which resulted in prompt and complete clearing of the symptoms and the x-ray abnormalities. Experience with the first case led to the correct diagnosis in a 5-month-old infant with strikingly similar symptoms and roentgen findings. Cineangiocardiography demonstrated prompt filling of 2 branches of the pulmonary artery to the right lung, a delay in passage of the contrast material through the smaller vessels to the left lung, and a patent ductus arteriosus. Again the response to ligation of the ductus was dramatic. The third patient, an 11-year-old boy, had a continuous murmur and other clinical findings typical of patent ductus arteriosus; all roentgen evidence of cardiopulmonary abnormality disappeared promptly after ligation of the ductus.

It is proposed that overaeration of the left lung, associated with apparent diminution of the vasculature within it, is a valuable x-ray finding suggesting the presence of a large patent ductus arteriosus. The mechanisms responsible for the changes are not clear.

Correlative Study of Intrarenal and Total Renal Blood Flow Measurements in the Dog

William F. Geber, Vermillion, South Dakota

The total and intrarenal blood flows were studied continuously and simultaneously by the use of direct and indirect methods. By the simultaneous use of both methods, it is possible to estimate intrarenal blood flow and to distinguish between blood flow and blood distribution within and between the cortical, intermediate, and medullary areas. A wide variety of chemical moieties were injected into the renal artery to determine the vascular responses of the 3 areas. Each injected chemical brought about a distinctive intrarenal vascular response, although similarities did

exist between responses recorded from physiologically related compounds. Stimulation of the intact renal nerves and the intact and cut vagus nerves indicated a direct influence of the renal nerves on the renal vasculature and both an indirect and a direct influence of the vagal nerves.

Incidence of Congenital Heart Disease in a Cross-Sectional Study of the Twin Population of the North American Continent

Goffredo G. Gensini, Salvatore Di Giorgi, Ann E. Kelly, and Frances A. Massa, Syracuse, New York

An extragenetic mechanism has been blamed by some as the cause of congenital heart disease, whereas others have stressed the importance of hereditary factors. At the present time, however, the majority of congenital heart disease cannot be readily explained on the basis of either the environmental or genetic theory. Widespread investigations of nature's own control group, that is to say, the study of twins and multiple births, may offer some help for the solution of this obscure and pressing problem.

A significant percentage of the twin population of the United States of America and Canada has been surveyed by the authors through the help of the National Mothers of Twins Clubs. In addition, the files of 4 American and Canadian medical institutions have been reviewed for twins with congenital heart disease. Preliminary results of this investigation further substantiate the high degree of discordance, already reported in the literature, existing among monozygotic and dizygotic twins insofar as cardiac malformations are concerned.

Furthermore, our results seem to stress the role of an extragenetic "triggering" mechanism, probably resulting in fetal ipoxia and producing cardiovascular anomalies in the offspring of genetically biased parents. Further experimental and clinical investigations are required.

At the present time, by comparing the data deriving from the affected child with those from his normal twin and taking into account the maximum deviation to be expected among normal twin pairs, it has been possible to assess accurately the severity of the lesion and either recommend or rule out its surgical correction.

Left Ventricular Function Following Fibrillatory Cardioplegia (P)

Thomas O. Gentsch, Parry B. Larsen, Michael Hume, and William W. L. Glenn, New Haven, Connecticut*

The competence of the left ventricle to respond to increased work loads may be expressed as a function curve relating stroke work to ventricular filling pressure. In view of the work of others demonstrating depressed ventricular performance following potassium, acetylcholine, anoxic and hypothermic arrest during cardiopulmonary bypass, a study of the effects of induced ventricular fibrillation on left ventricular function was done. Aortic and left atrial pressures and heart rate were measured and cardiac output determined by the thermal dilution method. Left atrial pressure was raised by transfusion in increments and ventricular stroke work determined at several levels of left atrial pressure. Comparison of pre- and postperfusion ventricular function curves revealed no depression after adequate cardiopulmonary bypass alone. Similar studies following 30 to 45 minutes of induced fibrillatory cardioplegia also demonstrated no adverse effect on ventricular function providing perfusion was physiologic. A most important requisite to maintenance of ventricular competence is decompression of the ventricular chambers by left auricular sump or direct left ventricular sump if the mitral valve proves competent. To date, induced fibrillation has been used to produce 69 periods of cardioplegia in 59 patients with acquired or congenital cardiac defects. Periods of cardioplegia ranged from 1 minute to 117 minutes and averaged 30.5 minutes. Induced ventricular fibrillation has produced no clinically observed adverse effect on resuscitation or ventricular performance. It has been concluded that induced ventricular fibrillation is a safe method of cardioplegia without adverse effects on ventricular function if cardiac chamber dilatation is prevented and perfusion is adequate.

Sound Spectrum of the First and Second Heart Sounds

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A new technic for the measurement of heart sounds has been developed at I.B.M., Kingston, New York. This computor method permits the study of the spectrum of heart sounds with a clarity and accuracy not available by other methods.

A total of 354 spectra of the first heart sound, as recorded at the pulmonic area, of 34 adult healthy males were measured and statistically analyzed. A similar analysis was made of the second heart sound.

This represents the initial phase of an automatic process for differentiating normal from abnormal heart sounds. This method is called spectral temporal and mass phonocardiography.

Biochemical and Enzymatic Changes in Atrial Fibrillation

Menard M. Gertler and Joseph D. Cohn, New York, New York

Biochemical investigations on atrial musculature have been limited by the difficulty of obtaining satisfactory atrial tissue for analysis. Atrial fibrillation was produced in dogs by faradic stimulation and application of mecholyl. The dogs were maintained during open-chest surgery by means of artificial respiration through a tracheostomy tube. The left auricle was removed prior to the establishment of atrial fibrillation and served as control tissue. After atrial fibrillation was maintained for 90 minutes, the right auricle was removed and analyzed.

Initial experiments have indicated 2- to 3-fold increases in the level of citric acid in the fibrillating auricle; α-ketoglutaric acid levels appear to remain unchanged, $Q^{N}_{O_2}$ values, with succinate as substrate in the fibrillating auricle, appear to be significantly lower than in the control tissue; isocitric dehydrogenase activity appears to be unchanged in the fibrillating auricle.

These observations are in keeping with the previously presented report on the failure of phosphorylation to be associated with the oxidation of citric acid by cardiac mitochondria.

Phonocardiographic Studies in Acyanotic Tetralogy of Fallot

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Phonocardiographic studies were made in 10 patients diagnosed as having acyanotic tetralogy of Fallot from adequate clinical and hemodynamic data. Pansystolic ejection murmurs were recorded in all, and in 7 patients, were right ventricular systolic pressure exceeded 80 mm. Hg, such murmurs were maximal in the second and third left intercostal spaces parasternally. The murmur configuration was usually attenuated initially and diamond-shaped with early crescendo, differing from that seen in the tricuspid area, where the murmur was more prominent initially and irregular. An apical flow murmur was recorded once.

The first sound was not delayed or accentuated. The second sound was abnormally split, and on unforced expiration A_2 to P_2 varied from 0.04 to 0.09 second. The aortic component was normal. The pulmonic component was normal or small in valvular stenosis and very small in infundibular stenosis. Pulmonary ejection sounds were recorded in 4 patients with valvular stenosis. Third or fourth heart sounds were common in those patients with the mildest degree of pulmonic stenosis.

The phonocardiogram in acyanotic tetralogy of Fallot usually demonstrated the murmur of moderate classic tetralogy of Fallot and the sounds of mild to moderate pulmonic stenosis. A ventricular septal defect could only be suspected by a different murmur configuration lower down the left sternal border. When the murmur appeared to be predominantly that of ventricular septal defect, the only clue to pulmonic stenosis was diminution of the pulmonic component of the second sound, where the stenosis was infundibular.

Exercise Performance Before and After Conversion from Atrial Fibrillation to Sinus Rhythm

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Exercise studies were performed in 11 subjects before and after conversion from atrial fibrillation to sinus rhythm. Duplicate studies in 8 cardiac subjects (6 in fibrillation and 2 in sinus rhythm) served as controls. Exercise consisted of treadmill walking at 1.7 m.p.h. at a 10 per cent grade. Heart rate, ventilation, oxygen consumption, alveolar (end-tidal) CO_2 tension, and oxygen debt were measured. In 2 converted and 4 control subjects, cardiac outputs were also measured. In spite of heavy digitalization, mean exercise heart rate was 151 per minute during atrial fibrillation; following conversion, mean heart rate fell to 109. After conversion, mean cardiac output with exercise was 1.8 L./min. higher (25 per cent) and stroke volume 45 ml. higher (91 per cent) than during atrial fibrillation. Physical fitness indices (method of Bruce) averaged 4 points higher following conversion. All these changes were significant at the 5 per cent level or below, as compared to duplicate studies in the control subjects. Mean ventilation fell 6.6 L./min. (18 per cent), and alveolar CO_2 tension rose 4 mm. Hg following conversion, but these changes were not significantly greater than changes in the control subjects. Oxygen debt showed no consistent changes. It is concluded that conversion to sinus rhythm improves exercise performance with the most striking changes occurring in heart rate and stroke volume.

Circulatory Effects of Long-term Norepinephrine Infusion

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Hemodynamic mechanisms of norepinephrine shock and norepinephrine refractoriness were studied in dogs given a 2-hour infusion of norepineph-

rine (4 to 14 μg./min./Kg.). Measurements were made of blood pressure (BP), cardiac output (CO) by the dye-dilution technic, central venous pressure (CVP), total peripheral resistance (TPR), and hematocrit.

In 9 experiments, after a contrived BP rise of 50 mm. Hg, the pressure tended to fall after 10 minutes. By the end of the infusion, BP was usually below control levels despite increasing norepinephrine and fell still more on stopping norepinephrine. The output first rose in 6 experiments (overall control 212; at 30 minutes 242 ml./min./Kg.). It was below control by 105 minutes in 6 of 6 surviving dogs (average 130 ml./min./Kg.). TPR was variable; it rose at some time in 7 and was above control in 4 of 6 animals before stopping infusion. CVP remained at or above control in all but 3. The ratio CO/CVP + 5 rose initially but fell by infusion end in 7 of 9. In 10 additional experiments, these trends were confirmed, and dextran infusion produced only slight increases of BP and CO. Hematocrits rose in 6 experiments where measured. In 5 open-chest experiments, pulmonary artery pressure rose strikingly in only 1 instance.

It is concluded that much of BP rise in dogs during norepinephrine infusion is due to CO rise, which is not sustained. CO fall is presumably myocardial, in view of trend to higher CVP and smallness of infusion response.

Further Clinical Evaluation of α-Methyl-Dopa

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Previous studies investigating the inhibitory effects of DL α-methyl-dopa (α-MD) on aromatic amino acid decarboxylation revealed that this agent possessed hypotensive properties. Continued investigation has been directed toward this agent's mechanism of action and its usefulness in the therapy of hypertension. Short-term oral administration of α-MD to 12 hospitalized hypertensives resulted in moderate lowering of the mean recumbent pressure (14 mm. Hg ± S.E. 4.1) and a greater effect on mean standing pressure (34 mm. Hg ± S.E. 3.5). Lowering of blood pressure was also produced in 7 patients who received 500 to 1,000 mg. of α-MD intravenously; the effects began within 2 hours, were usually maximal in 6 hours, and persisted for 12 to 24 hours. Plasma concentrations following infusion fell rapidly to negligible levels at 6 to 8 hours. Further studies have demonstrated that both the biochemical and physiologic properties are found only in the levo isomer of α-MD.

The effectiveness of prolonged therapy with racemic and levo α-MD, alone or in combination with chlorothiazide, was evaluated in 25 clinic patients with primary hypertension for periods of 3 to 20 months. Neither parasympathetic side-effects nor tolerance was observed. Initial drowsiness lasting 1 to 3 days may occur, diminishing then to a persistent tranquilizing effect in most patients. In 9 of these patients, the effect of adding α-MD to chlorothiazide was compared to the hypotensive effect of chlorothiazide and α-MD placebo. The average reduction in mean recumbent pressure produced by addition of α-MD was 22 mm. Hg (± S.E. 6.8) and 31 mm. Hg (± S.E. 9.2) for mean standing pressure.

Continuous Ambulant Electrocardiograms and Their Analysis—Clinical Observations Using the Electrocardiocorder and Avsep Analyzer (P)

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The electrocardiocorder and Avsep analyzer are new instruments making it conveniently possible to obtain and analyze long-duration, continuous records of human electrocardiographic activity under normal physical and emotional conditions. By comparison, orthodox electrocardiography provides too short a sample to be representative of real-life situations. These new methods provide continuous electrocardiographic information in the form of a "movie" on an oscilloscope showing a dynamic PQRST pattern, which remains fixed when successive electrocardiograms remain the same and which slowly varies its form as abnormal clinical conditions occur, e.g., angina patients shoveling snow, etc.

This technic has been tried with 150 patients, and much valuable information not obtainable by orthodox electrocardiography was acquired. Progressive changes have been followed in detail during the period of classic anginal pain relieved by nitroglycerin. Moreover, similar changes have been observed in the absence of pain in situations previously associated with pain in the same patients. We have been able to confirm questionable diagnoses in certain anginal patients.

In normals, variations in the height of T waves were followed during eating, exercise, or excitement. Records taken before, during, and after surgery demonstrated interesting variations which became more or less stabilized during the anesthesia periods.

These clinical tests confirm that very useful information can be obtained without objectionable muscle interference during heavy exercise. The method shows considerable promise in evaluating patient tolerance under natural conditions and provides hitherto unavailable quantitative data on cardiac function.

Studies on the Determinants of the First Derivative of the Intraventricular Pressure Pulse in Man

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Observations in experimental animals have suggested that the rate at which ventricular pressure rises is a function of myocardial contractility. The first derivative of the ventricular pressure pulse was continuously computed by means of an electronic differentiating circuit in 27 patients. In order to avoid the artifacts inherent in pressures measured by means of standard catheter-manometer systems, these studies were confined to pressures obtained from a catheter with a high-fidelity micromanometer mounted at its tip (Dallons-Telco) or by puncture of the ventricle with the manometer directly attached to the needle. The peak first derivative (maximum rate of pressure rise) in patients without hemodynamic abnormalities ranged between 800 and 1,400 mm. Hg/sec. in the left ventricle and between 200 and 300 mm. Hg/sec. in the right ventricle. Muscular exercise, isopropylnorepinephrine, norepinephrine, and atropine induced tachycardia and resulted in striking (up to 3-fold) increases in the peak derivative. Beat-to-beat changes in ventricular filling in patients with atrial fibrillation produced similar changes. In the control state, the peak derivative in either ventricle demonstrated a linear correlation with the peak systolic pressure. The maximum value observed in the left ventricle was 3,240 mm. Hg/sec. in a patient with aortic stenosis and 820 mm. Hg/sec. in the right ventricle of a patient with pulmonic stenosis. In patients with a variety of cardiac abnormalities, the peak derivative in the basal state appeared to be dependent on the pressure load rather than the flow load imposed on the ventricle, but the derivative may also be affected acutely by changes in myocardial contractility.

Effect of Hypothermia on the Pulmonary Circulation (P)

Robert H. Goetz, Michael Rohman, Ronald Dee, Verena M. Goetz, and David State, New York, New York

Few studies have concerned themselves with the effect of hypothermia on the pulmonary vascular bed. With the widespread use of hypothermia, this aspect may be of greater practical importance than has hitherto been recognized. The changes occurring in the heart itself make analysis of the vascular effects of hypothermia difficult in the intact animal. The present study, therefore, makes use of the technic of separate perfusion of the systemic and pulmonary circulations, by means of 2 extracorporeal pumps, which allows changing the temperature of the blood in the 1 circuit while that in the other is kept constant.

When the temperaure of the blood in the pulmonary circuit of a normal dog was changed from 38 to 20 C., pulmonary artery pressure rose, and systemic blood pressure dropped. Since the blood flow remained constant in both the systemic and pulmonary circuits, the response was interpreted as a rise and a fall in resistances, respectively. The opposite effects were recorded on changing the temperature of pulmonary perfusate from cold to warm.

Whereas the effect on the pulmonary vascular bed confirms findings of earlier investigators, the fall of the systemic circulation has not previously been reported. It could be abolished by cutting of the vagi and by the administration of a sympathicolytic drug into the systemic circulation. It was not abolished by atropine. It was concluded, therefore, that we are dealing with a reflex mechanism which originates in the pulmonary vascular bed, the afferent pathway of which is transmitted by the vagus whereas the efferent limb is found in the sympathetic.

Removal of Individual Free Fatty Acids by the Normal and Diabetic Myocardium and Skeletal Muscle and Their Mobilization by Adipose Tissue

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Simultaneous blood samples were obtained from different sites in anesthetized dogs. The plasma was separated, free fatty acids determined chemically by Dole's method, and also analyzed gas chromatographically after removing phospholipids, cholesterol, tri-, di-, and monoglycerides.

As has been found before, myocardium removed palmitic, palmitoleic, stearic, oleic, and linoleic acids. Insulin (1 unit/Kg.) greatly diminished the absolute and percentage uptake of most fatty acids 15 minutes after its administration. In preliminary experiments, the myocardium of alloxan diabetic dogs removed the same fatty acids in different proportions. The uptake of oleic acid seemed to be decreased. Insulin reduced the uptake of some of the free fatty acids by the diabetic myocardium.

Skeletal muscle during direct electrical stimulation removed the various free fatty acids. Oleic acid was taken up in greatest quantities.

The total and free fatty acid composition of subcutaneous adipose tissue was also analyzed in normal dogs. In both, there was a higher percentage of oleic and linoleic acids and a lower percentage of palmitic and shorter chain fatty acids than found in the plasma. The vein draining the same

adipose tissue did not reflect the abundance of oleic and linoleic acids.

Evaluation of the Krypton^{85} Inhalation Test for the Detection of Left-to-Right Cardiac Shunts

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The detection, localization, and quantification of circulatory shunts is of fundamental importance in the evaluation of patients with congenital cardiac malformations. Although a variety of technics have been developed, little specific information about their reliability is available. Krypton^{85} inhalation tests were carried out in 323 patients, in all of whom the diagnosis was firmly established, and the results were analyzed. Blood samples were withdrawn simultaneously and at a constant rate from the right side of the heart and a systemic artery, while the patient inhaled a Kr^{85}-air mixture. The ratio of the radioactivity in blood obtained from the right side of the heart to that obtained from a systemic artery was determined and expressed as a percentage. In the 161 patients subsequently proved to have left-to-right shunts, the results of the test ranged from 13 to 113 per cent. In the 162 patients without cardiac shunts, the results ranged from 0 to 12.2 per cent. The Kr^{85} test may thus be employed with confidence for determining the presence or absence of a left-to-right shunt. In addition, when the test is successively performed in the pulmonary artery, right ventricle, and right atrium, the site of entry of the shunt into the right side of the heart may be correctly localized.

Cor Pulmonale in Cystic Fibrosis of the Pancreas (P)

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Cor pulmonale is frequently observed at autopsy in patients with the pulmonary complications of cystic fibrosis. The present study was designed to identify the physiologic mechanisms involved in the pathogenesis of pulmonary hypertension and cor pulmonale in this disease.

Sixteen patients, 6 to 22 years of age, with varying degrees of pulmonary disability were studied. Pulmonary blood pressures (cardiac catheterization) and flow (Fick principle) were measured during rest, exercise, and high-oxygen breathing. Fourteen of the 16 patients had physiologic evidence of moderate to severe airway obstruction and maldistribution of inspired gas. Despite this evidence of bronchial disease, only 2 of the 14 (aged 6 and 18 years) had pulmonary hypertension (resting mean pressures of 39 and 28 mm. Hg, respectively; exercise mean pressures of 64 and 55 mm. Hg, respectively). These subjects were the only 2 with appreciable systemic arterial hypoxemia (oxygen saturations of 75 and 78 per cent, respectively); relief of the hypoxemia while breathing 40 per cent oxygen lowered the pulmonary arterial mean pressure by 13 and 14 mm. Hg, respectively, with no measurable reduction in cardiac output or minute ventilation. Sustained relief of hypoxemia in the 6-year-old patient, following successful treatment with antibiotics and a mechanical respirator, resulted in a return of pulmonary arterial pressure to near-normal values.

These results indicate that in the present study, hypoxemia, rather than a specific ventilatory defect or the duration of the disease, is the major determinant of cor pulmonale in cystic fibrosis.

Influence of Exercise and Autonomic Tone on the Duration of Left Ventricular Isometric Contraction (P)

Ira M. Goldstein, William J. deGroot, and James J. Leonard, Galveston, Texas

The isometric contraction period has been assigned a major role in myocardial energy utilization. However, little information is available concerning the factors which control the duration of this period. Isometric contraction, together with systolic ejection and Q1 time, was measured in 21 normal, young volunteers at rest and during various maneuvers which produce tachycardia. Mechanical systole was measured from the first sound to the aortic closure sound of the phonocardiogram. Ejection period was measured from simultaneously recorded carotid pulse tracings. Isometric contraction was determined by subtracting the latter from the former.

In 14 subjects, isometric contraction time was measured before and at various intervals after moderate exercise. Heart rate increased to 94 from a basal level of 73 beats/min. and returned to resting levels after 5 minutes. Isometric contraction time decreased significantly from a resting level of 0.040 to 0.018 second ($p < 0.01$) and did not return to normal until after 10 minutes of rest. In contrast, atropine and ganglionic blockade with trimethaphan camphorsulfonate, while increasing heart rate significantly (71 to 108 beats/min.), had only a slight, but not significant (0.051 to 0.045 second) effect on isometric contraction time. Epinephrine increased heart rate and decreased isometric contraction time to levels similar to those seen in the postexercise state. Heart rate of itself appears to exert only a slight effect on the isometric contraction period. Results of exercise and catecholamine infusion are similar, suggesting adrenergic activity as the principle controlling factor of this phase of the cardiac cycle.

Mechanism of "Pulsus Paradoxus" During Acute Pericardial Tamponade (P)

Richard J. Golinko, Abraham M. Rudolph, Emile M. Scarpelli, and Norman L. Gootman, New York, New York*

This study was designed to investigate the mechanism of pulsus paradoxus during pericardial tamponade. Polyvinyl catheters were directly inserted into pulmonary vein, left atrium, and left ventricle through a left thoracotomy. Intrathoracic pressure was measured with an intraesophageal balloon. The chest was closed and pressures in the various segments recorded during spontaneous breathing and inspiratory obstruction with varying degrees of pericardial tamponade. In the control animal without pericardial tamponade, pulmonary venous and left atrial pressures fluctuated considerably with respiration. A consistent pressure gradient between pulmonary vein and left atrium existed during all phases of the respiratory cycle but was greater during expiration. With pericardial tamponade, pulmonary venous pressure continued to show wide respiratory fluctuations, whereas left atrial pressure fluctuations were greatly reduced. In all experiments, pulmonary venous pressure was less than left atrial pressure during inspiration. During expiration, the gradient between pulmonary vein and left atrium was maintained as in the control but reduced in magnitude. In the control animal, intrapericardial pressure varied with respiration and closely paralleled intrathoracic pressure. During tamponade, intrapericardial and left atrial pressures were similar, and fluctuations with respiration were greatly reduced.

These studies suggest that the mechanism for pulsus paradoxus resides in the altered relationships between pulmonary venous and left atrial pressure during the respiratory cycle. The pulmonary venous pressure follows intrathoracic pressure, whereas left atrial pressure follows intrapericardial pressure, resulting in a reversal of the normal pressure gradient during inspiration. This interferes with left atrial filling even more than usual during inspiration, exaggerating the drop in stroke volume and arterial pressure.

Metabolic Acidosis in Severe Cyanotic Congenital Heart Disease (P)

Norman L. Gootman, Emile M. Scarpelli, and Abraham M. Rudolph, New York, New York*

The ability of infants with severe hypoxia and arterial oxygen saturation levels below 50 per cent to survive for several months or longer is well recognized. These infants have a markedly reduced actual or effective pulmonary blood flow. Studies of pO_2, pCO_2, and pH on systemic arterial and pulmonary venous blood were made in 4 children with very severe cyanosis in order to examine the mechanisms by which the patient adapted to the severe degree of hypoxia. In 1 of these children, a boy with tetralogy of Fallot, measurements were made during an acute cyanotic spell.

The arterial pO_2 was markedly reduced to levels of 24 to 35 mm. Hg, whereas pulmonary venous pO_2 was normal. The most striking observation was that of a normal or reduced systemic arterial pCO_2 in all 4 children, including the child with the acute cyanotic spell (34 to 41 mm. Hg). The pulmonary venous pCO_2 was moderately to markedly reduced to levels of 16 to 27 mm. Hg, probably as a result of the reduced pulmonary blood flow and resting hyperventilation. Systemic arterial pH was decreased in all patients to levels of 7.24 to 7.35, indicating the presence of acidosis, which in the face of normal pCO_2 was metabolic in type. The pulmonary venous pH was normal or slightly elevated.

The presence of metabolic acidosis in severe chronic cyanotic congenital heart disease, as well as in the acute cyanotic spell, raises the possibility that under severely hypoxic conditions, children may utilize metabolic pathways which differ from those in normal individuals.

Cardiac Output Response to Changes in Posture and Exercise

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The isotope-external counting method was adapted for determination of cardiac output during moderate exercise to aid in the evaluation of young and middle-aged adults referred for a variety of abnormal signs suggesting heart disease. Output was measured in supine and sitting positions and during exercise on a stationary bicycle. Changes in flow, rate, and stroke volume were each compared with patient's age, physical condition, exercise participation, smoking habits, type of flying assignment, altitude of home base, severity of cardiac or noncardiac referral problem, and maximum exercise tolerance as measured on an inclined treadmill.

Cardiac index dropped significantly on change from supine (average 3.8 L./min./M.^{2}) to sitting position (average 2.9). During "steady state" of exercise, with the same work assignment for all patients, average index was 5.9 with a greater spread of results than in either of the other sets of values. Absolute and percentage increase over sitting level could be fairly well correlated with each individual's exercise habits and treadmill performance. Comparisons with patient's age, cardiac

disorder, and smoking habits were not statistically valid in this group.

When compared to baseline sitting values, exercise was accompanied by an increase in stroke index in all patients, the degree varying, in general, with the amount of cardiac index elevation. The simplicity of the external counting technic and now its use during exercise make it a useful objective test in evaluating an individual's cardiac adaptations to exercise.

Level of Significance for the Diagnosis of Ventricular Septal Defect with Left-to-Right Shunt

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Left-to-right shunt (L-R) through a ventricular septal defect (VSD) is suspected on demonstrating a significantly higher blood oxygen saturation within the right ventricle (RV) compared to the right atrium (RA). This study evaluated the power of oxygen analysis as an isolated diagnostic technic. A combination of clinical findings, x-rays, electrocardiography, vectorcardiography, cardiac catheterization with oxygen analysis, hydrogen indicator method, and selective angiocardiography was employed to evaluate and classify anatomically 208 consecutive patients. There were 57 patients with a VSD as the only L-R shunt, and 55 patients had no shunt. The average of at least 4 blood analyses from the RV outflow tract was compared to the average of 4 specimens from the RA. The difference between means was standardized (t-test) and the level of significance determined from the t-distribution. Of the 57 with VSD as the only L-R shunt, the difference between means was *not* significant at the 1 per cent level (false negative) in only 1 patient. Of 55 patients with no shunt, the difference in means was significant at the 1 per cent level (false positive) in only 1 patient. It is concluded that oxygen data, properly accumulated and analyzed, employing the 1 per cent significance level as critical, is as powerful as any available technic for detection of L-R shunt in VSD.

Effect of Glucose Administration on Free Fatty Acid Mobilization in Hyperthyroidism

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Serial serum free fatty acid concentrations (FFA) were determined in 7 hyperthyroid patients and 9 normal subjects during a standard 100-Gm. oral glucose tolerance test. Mean fasting FFA was 1,342 μEq./L. in the hyperthyroid group and 609 μEq./L. in the euthyroid patients. Following glucose administration, the mean of the maximum decrements in FFA was only 395 μEq./L. in the euthyroid group, contrasted with 1,139 μEq./L. in the hyperthyroid subjects. The magnitude of the observed decrease varied directly with the fasting level. Both groups reached similar mean values for the minimum absolute FFA levels, 200 μEq./L. in the euthyroid and 234 μEq./L. in the hyperthyroid subjects. This low level was attained at 1 hour and persisted until the end of the third hour when a return toward normal occurred. The mechanism of the accelerated FFA mobilization in hyperthroidism is uncertain. Thyrotropin, hyperthyroxinemia, and sympathetic overactivity have been implicated. Since glucose causes a marked fall in FFA, presumably without altering these 3 factors, their role is probably mediated indirectly. The glycogen-depleted liver in the thyrotoxic patient is unable to meet the increased demand of peripheral tissue for glucose during fasting. This is reflected in fat depots by breakdown of tissue triglycerides with release of FFA into the plasma. The accelerated FFA mobilization in the fasting, hyperthyroid patient is probably due to relative tissue starvation.

Studies of Mechanisms by Which Chlorothiazide Potentiates Ganglion-Blocking Agents

Murray A. Greene, Adolph J. Boltax, Edward E. Scherr, and Molly Niv, Bronx, New York

Eight hypertensive and 7 normotensive patients were studied in the supine position and postabsorptive state. The sequence of the experiment in each subject was as follows: (1) an initial control period, (2) Arfonad-induced hypotension, (3) re-establishment of control state, (4) repetition of (2) and (3), (5) administration of 1.0 Gm. chlorothiazide intravenously, and (6) Arfonad-induced hypotension approximately 1 hour later. Cardiovascular dynamics were evaluated during each phase. Total plasma, blood volumes, and fluid balances were measured before each Arfonad injection.

Arfonad, administered before chlorothiazide, reduced systemic arterial pressures in all hypertensive and in 5 normotensive patients. These changes were due to decreases in peripheral resistances, or cardiac outputs, or both. Arfonad, administered 1 hour after chlorothiazide, caused significantly greater reductions in systemic arterial pressures in 4 hypertensive and 3 normotensive subjects. These changes were due to greater reductions in peripheral resistances, or cardiac outputs, or both. In general, reductions in cardiac outputs were due to falls in stroke outputs. Right-heart diastolic pressures were normal in all but 1 (hypertensive) subject and did not change significantly at any time. Decreases in total blood volumes due to blood sampling technics were small

and bore no relation to the presence or absence of potentiation. There were no primary changes in plasma volumes 1 hour after chlorothiazide.

The results suggest that the potentiation of ganglion-blocking agents by chlorothiazide in some subjects may not depend on oligemia but, rather, may involve combined effects, direct or indirect, of the drugs on vascular walls. In addition, this phenomenon is not restricted to the hypertensive state.

Effects of Intravenous Lanatoside-C on Cardiodynamics in Patients with Mitral Stenosis and Regular Sinus Rhythm

Murray A. Greene, Arthur Gordon, and Adolph J. Boltax, Bronx, New York

This study is concerned with the acute effects of intravenous lanatoside-C on cardiovascular dynamics in 7 patients with mitral stenosis and regular sinus rhythm. Control data revealed that mild to severe pulmonary arterial hypertension was present in 6 patients, pulmonary "wedge" pressures were elevated in 4 of the 5 patients in whom they were measured, cardiac outputs were depressed in all patients, and right ventricular decompensation, as indicated by an elevation in end-diastolic pressure, was present in 4 patients. Pulmonary vascular resistances were elevated to variable degrees in all patients. The cardiodynamic responses to the administration of lanatoside-C were distinguished by 3 patterns. In 1 pattern, improvement in right ventricular function (abnormal initially) resulted in an increased output into a vascular bed from which outflow was obstructed. Right ventricular end-diastolic pressure fell, cardiac output and stroke volume rose, and pulmonary arterial systolic pressure rose. A second pattern demonstrated the salutary effects of bradycardia with its attendant increase in diastolic time. This permitted greater emptying of the pulmonary vascular bed, which, in turn, caused reductions in pulmonary arterial diastolic and mean pressures and pulmonary "wedge" pressure. Stroke volumes increased as phenomena secondary to the bradycardias. Cardiac output increased in that subject who had improvement in right ventricular function. When both improvement in right ventricular function and bradycardia occurred in the same subject, the latter exerted the dominant influence on pulmonary vascular pressures. The third pattern was characterized by an absence of hemodynamic changes after administration of lanatoside-C.

Baseline for Antihypertensive Therapy

Raymond F. Grenfell, Arthur H. Briggs, and William C. Holland, Jackson, Mississippi

From a statistically analyzed double-blind study begun in 1956, a base has been developed in outpatients for oral and parenteral hypotensive agents.

Parenterally, 41 receiving placebo every 2 weeks had a decrease in systolic pressure for 59 weeks and diastolic pressure for 143 weeks. In 33, ergot alkaloids every 2 weeks caused a decrease in systolic pressure for 47 weeks and diastolic pressure for 143 weeks.

Orally, 15 receiving 3 placebo tablets daily had no change in pressure. In 12, a mixture containing 4.98 mg. dihydroergocornine methanesulfonate, 4.98 mg. dihydroergokryptine methanesulfonate, and 4.98 mg. dihydroergocristine methanesulfonate was given daily with a decrease in systolic and diastolic pressure. The third group took 15 mg. dihydroergocornine methanesulfonate daily without a decrease in systolic or diastolic pressure. The fourth group was given 0.50 mg. reserpine daily with a decrease in systolic and diastolic pressure. The fifth group took 1 capsule containing 12.5 mg. rauwolfia, 0.1 mg. protoveratrine, 2.5 mg. phenoxybenzamine hydrochloride, with the dose being increased weekly. Then, double the above strength was given and the dosage increased weekly, with a decrease in systolic and diastolic pressure. The sixth group took 45 mg. phenobarbital daily without a decrease in systolic or diastolic pressure. The seventh group took 30 mg. thioridazine daily with a decrease in systolic pressure but only in weeks 3, 5, and 6 in diastolic pressure. The eighth group was given 30 mg. benzyl hydrazine daily with a decrease in systolic and diastolic pressure.

Prognosis and Anticoagulant Therapy in Acute Myocardial Infarction

George C. Griffith, Balakrishna Hegde, and David Leak, Los Angeles, California

A homogenous group of over 1,000 patients with acute myocardial infarction were treated in the Los Angeles County Hospital in a year with differing regimens and standards of care. The effect of anticoagulants on mortality during acute myocardial infarction was assessed.

An initial group of 200 patients was chosen at random. The diagnosis of myocardial infarction was established by electrocardiographic tracing, serum transaminase, and/or autopsy. The overall mortality rate in this group was 53.4 per cent. The mortality age distribution agrees well with previously published reports. The following factors were associated with a significantly increased mortality: a previous history of dyspnea on exertion, shock, cardiac failure, and all severe arrhythmias excluding first-degree heart block. The

presence of any of these factors within 48 hours of admission was the basis of defining the "bad risk." In the absence of these factors (i.e., "good risk"), the overall mortality was 17.9 per cent and in bad-risk patients 70.7 per cent. Only 4 patients originally classified on this basis changed from good risks to bad risks.

The use of anticoagulant therapy was classified as (1) adequate, (2) inadequate (according to established criteria), and (3) absent. The effect of anticoagulant therapy in 153 patients who survived 48 hours was assessed: 91 received anticoagulants, of whom 34 were classified as inadequately treated. In good-risk patients receiving anticoagulant therapy, the overall mortality was 10.4 per cent, compared with 29.4 per cent not receiving anticoagulants. In bad-risk patients receiving adequate anticoagulant therapy, the mortality rate was 39.3 per cent, compared with 48 per cent with inadequate therapy and 80 per cent in those not receiving anticoagulant therapy.

Ventricular Septal Defect in the Adult Age Group (P)

Sylvia P. Griffiths, New York, New York, Beverly C. Morgan, San Antonio, Texas, A. Gregory Jameson, and Sidney Blumenthal, New York, New York

Information regarding the prognosis of patients with ventricular septal defect in adult life is sparse. The clinical course in this age group requires elucidation. Thirty-three patients with this defect, ranging in age from 17 to 63 years, have been observed. Several were erroneously considered to have rheumatic heart disease. The diagnosis was first made at necropsy in 6. In the remaining 27 patients, cardiac catheterization was performed; in 5, it was repeated at intervals of 5 to 12 years. Measurements of right ventricular and pulmonary artery pressures indicated (1) normal values in 15, (2) right ventricular hypertension and pulmonic stenosis in 3, and (3) pulmonary hypertension in 9 (in 1, recatheterization documented increasing pulmonary pressure). Aortic insufficiency was a complicating lesion in 1 patient.

Six patients succumbed during the follow-up period. Three had normal pulmonary artery pressure: 2 died of congestive heart failure at 27 and 42 years (both had previously been successfully treated for bacterial endocarditis) and 1 of unrelated cause at 33 years. Three patients with pulmonary hypertension died; 2 following open-heart surgery at 18 and 35 years (severe pulmonary vascular changes were noted at necropsy in both) and 1 in an accident at 45 years.

Approximately half of the patients in this series reached adult life with normal pulmonary artery pressures; the oldest is an asymptomatic 48-year-old man. Bacterial endocarditis in previously symptom-free patients predisposed to progressive myocardial failure despite a prompt bacteriologic cure.

Effect of Acetylstrophanthidin on Myocardial Glucose Utilization in the Normal Dog (P)

Douglas M. Griggs, Jr., Dorothy A. Piatnek, and Robert E. Olson, Pittsburgh, Pennsylvania

By combining coronary sinus catheterization with continuous administration of a radioactive substrate, it was possible to study the effect of acetylstrophanthidin on substrate utilization in the intact heart. Glucose U-C^{14} was infused in trace amounts into the anesthetized, postabsorptive dog to maintain the body glucose pool at a constant specific activity. Serial blood samples for $C^{14}O_2$ specific activity and CO_2 content were collected simultaneously through cardiac catheters from the coronary sinus, the pulmonary artery, and the femoral artery at intervals during the control period and following the administration of 0.025 mg./Kg. of acetylstrophanthidin.

Results from 4 experiments, in which there were no significant changes in electrocardiogram, heart rate, or aortic pressure attributable to acetylstrophanthidin, showed a sharp rise in coronary sinus $C^{14}O_2$ specific activity without a change in CO_2 content. Peak values were obtained 30 minutes after the drug, following which there was a decline toward the baseline. In an experiment in which saline was injected in place of the drug, no rise in coronary sinus $C^{14}O_2$ specific activity occurred. Myocardial glucose utilization calculated from the radioactivity data and an assumed coronary flow of 100 ml./min./100 Gm. of myocardium revealed an increase from 5.1 ± 1.6 to 9.9 ± 1.7 mg. glucose/min./100 Gm. (94 per cent) following acetylstrophanthidin.

It is concluded that myocardial glucose utilization is enhanced at the expense of other substrates by nontoxic amounts of acetylstrophanthidin. It cannot be implied that this effect of the drug is related to its positive inotropic action.

Late Results Following Mitral Replacement with the Starr-Edwards Prosthesis (P)

Herbert E. Griswold, Albert Starr, J. David Bristow, Victor D. Menashe, and Zaven A. Adrouny, Portland, Oregon

This report summarizes the clinical and hemodynamic results in 9 patients who have survived from 1 to 8 months after operation. The age range was 28 to 53 years. Three patients had

mitral stenosis with severe calcification, and 6 had mitral insufficiency. Three patients were male and 6 female. Before surgery, the patients were classified functionally as class III or IV.

All patients had low, fixed cardiac outputs with left atrial and pulmonary hypertension before surgery. The preoperative mean left atrial pressures varied from 17 to 42 mm. Hg. After replacement of the mitral valve, the mean left atrial pressures varied from 8 to 18 mm. Hg. Patients who have completed convalescence are improved to class I or II.

Chest x-rays in the postoperative period demonstrated a consistent reduction in the overall cardiac size, as well as a decrease in the pulmonary vascular markings.

Two patients thus far have been studied by catheterization 4 months after surgery. Resting pulmonary artery pressures had decreased. The mean wedge pressures were 12 and 7.5 mm. Hg. The resting cardiac output was normal or slightly reduced and increased with exercise. Both had a moderate increase in pulmonary artery pressures with exercise without significant elevation of pulmonary wedge pressure. Thus, there is a persistent elevation of pulmonary vascular resistance.

In spite of longstanding, severe mitral valve disease, replacement of the mitral valve in class III or IV patients may result in excellent symptomatic and hemodynamic improvement.

Potential Preventability of First Attacks of Acute Rheumatic Fever in Children

Burton J. Grossman and Jeremiah Stamler, Chicago, Illinois

In the modern era, timely diagnosis and effective therapy of group A beta hemolytic streptococcal infections make possible the prevention of late nonsuppurative complications, e.g., rheumatic fever-rheumatic heart disease and glomerulonephritis. However, the possibility of subclinical streptococcal infections with minimal or no antecedent symptoms or signs leading to rheumatic fever-rheumatic heart disease remains a problem. This study was undertaken to quantitate the scope of this problem and, therefore, to estimate the present-day preventability of rheumatic fever. An analysis was made of 110 consecutive hospitalized cases of first attacks of acute rheumatic fever in children. Almost 90 per cent gave a history of a definite infection, in most cases respiratory in type, in the 6 weeks preceding the attack. About 60 per cent were seen by a physician. Throat cultures were done in only 10 per cent. Antibiotic therapy was utilized in 50 per cent, but in most cases the choice of drug and/or the duration of therapy did not correspond to American Heart Association recommendations for the treatment of acute group A beta hemolytic streptococcal infections. It may be concluded that in a majority of frank clinical rheumatic fever cases requiring hospitalization, the disease is preventable if parents and physicians are alerted to a sound approach to respiratory infections in children.

Split Renal Function Studies in Renovascular Hypertension

Jacob Grossman, Arthur G. Goldman, and Morris Wolfman, New York, New York

Separate ureteral catheterization for suspected unilateral renovascular hypertension has been performed in 27 patients. Earlier, subjects with parenchymatous renal disease whose pyelograms revealed a unilaterally smaller kidney were catheterized. More recently, patients with predominantly renal vascular disease have been studied in an effort to correlate the findings with those of renal arteriography and surgical exploration.

The studies included measurement of renal hemodynamics and urinary osmolarity and electrolyte excretion, followed by subsequent determination of $^{T}M_{PAH}$. Urine was also obtained from each ureter for albumin content and culture. During control periods, dilution was stimulated by moderate water loading; conversely, during $^{T}M_{PAH}$ determination, sodium loading response was measured. Excessive water was avoided to minimize the escape of urine around the catheter into the bladder.

On the basis of rigid criteria, 4 patients were nephrectomized. All exhibited a persistent fall in blood pressure to within normal limits; in 3, this occurred promptly. Surgery was withheld in other subjects because of bilateral renal involvement or some impaired function on the "normal" side. Functionally, ischemic kidneys exhibited significantly diminished renal hemodynamics, urinary flow, and sodium concentrations; increased osmolarity not due to electrolyte; and altered concentrating function. While analysis of bladder urine often permitted lateralization of its origin, bladder transport of water and electrolytes may complicate the procedure. However, by methods devised to correct for water transfer, bladder contribution to urinary composition may be established. Previous findings of passive diffusion of electrolyte and creatinine have been confirmed.

Pulmonary Vasoconstriction in Steers at High Altitude (P)

Robert F. Grover and John T. Reeves,† Denver, Colorado

Ten normal steers born at 3,500 feet were taken for 9 weeks to 12,700 feet on Mount Evans, Colo-

rado, where serial pulmonary arterial catheterizations were performed at 1, 2, 3, 6, 8, and 9 weeks. All steers developed marked pulmonary hypertension within 2 weeks. Mean pulmonary arterial pressures at the final measurement ranged from 50 to 109 mm. Hg. In contrast, sheep exposed to identical conditions showed virtually no elevation of their pulmonary arterial pressure. The rapid development of the pulmonary hypertension in cattle and the marked and immediate decrease in pulmonary arterial pressure following oxygen inhalation at high altitude implied that vasoconstriction due to hypoxia was a potent etiologic factor. In fact, comparison of the vasoconstrictive effect of acute hypoxia in the initial low altitude measurements (mean pressure rise from 30 to 39 mm. Hg) with the pressure fall with oxygen at high altitude (a mean fall from 68 to 50 mm. Hg at 3 weeks and from 124 to 74 mm. Hg at 9 weeks) indicated that both the immediately reversible and the relatively fixed components of the pulmonary hypertension increased with continued residence at 12,700 feet.

Pathologic and radiographic examination of the pulmonary vasculature in these steers, combining the injection technic of Short and the standard histologic staining methods, suggests that the primary lesion is muscular hypertrophy of the small pulmonary arterioles. It is concluded that this study brings important evidence to bear on the pathogenesis of hypoxia-induced pulmonary hypertension.

Equalization Rate, a Hemodynamic Method for Differentiation of Mitral Stenosis and Regurgitation (P)

Rolf M. Gunnar, John R. Tobin, Jr., Chicago, Illinois, Walter T. Goodale, and James A. Bougas, Boston, Massachusetts

Since repair of the insufficient mitral valve requires extracorporeal circulation and repair of the stenotic mitral valve does not, considerable effort has been directed toward the development of diagnostic methods which differentiate handicapped patients with predominant mitral insufficiency from those with predominant stenosis. A method has been devised which is based on the equalization rate of the pressure difference between left atrium and left ventricle in diastole.

Left atrial pressure, left ventricular pressure, and external phonocardiogram have been simultaneously recorded. The equalization rate is calculated from pressure-pulse contours by application of a straight line to left atrial pressure descent and left ventricular pressure increase, utilizing opening snap of the mitral valve to indicate onset of ventricular filling. The results, expressed in mm. Hg/sec., are related to cardiac output determined by the Fick principle. The pressure-pulse contours have also been analyzed by methods which utilize peak V-wave pressure, rate of Y descent, and mean left atrial pressure to calculate indices of mitral orifice function. The basic differences between equalization rate and these other methods of calculation are as follows: Equalization rate calculations include changes in left ventricular diastolic pressure and ignore V-wave peak and that portion of Y descent occurring prior to mitral valve opening.

Mitral orifice size and competence have been estimated during surgical repair in 20 patients, and equalization rate, when compared to other indices of mitral orifice function, has been found to provide the best correlation.

Instantaneous Increase in Cardiac Output at Onset of Muscular Contraction

Arthur C. Guyton and Ben H. Douglas, Jackson, Mississippi

These studies report an instantaneous increase in cardiac output resulting from purely mechanical effects of muscular contraction. This effect has been studied in 2 different ways: (1) Cardiac output was recorded continuously by means of an automatic Fick cardiac output recorder; the spinal cord was transected in the thorax, and the lower spinal cord was stimulated electrically at approximately L-1 to contract all the muscles of the lower body. (2) A cardiac bypass system was used in place of the heart, and the lower spinal cord was stimulated as above. With either of these 2 methods, sudden stimulation of the lower cord caused the cardiac output to rise to double normal within the next few beats of the heart. This effect also occurred when the animal was treated with enough hexamethonium to block the autonomic nervous system entirely, showing that it was not an autonomic response. To show that the effect is a purely mechanical one, approximately 50 per cent increase in cardiac output could be obtained by sudden onset of muscular massage in the lower abdomen and both legs. To explain the cause of the increased cardiac output, the mean circulatory pressure was measured before and after the onset of electrical stimulation. Electrical stimulation approximately doubled the mean circulatory pressure, presumably because of compression of intramuscular and intra-abdominal blood vessels. Such an increase in mean circulatory pressure has been pointed out previously to be one of the major factors regulating cardiac output.

Diagnostic Investigation of Hypertensive Patients with Suspected Unilateral Renal Valvular Disease (P)

Thomas E. Hair, Jr., Victor A. Politano, and Edward S. Orgain, Durham, North Carolina

Unilateral renal vascular disease is an infrequent yet important cause of hypertensive disease. Because it is potentially correctable by surgery, its presence must be suspected in each patient who exhibits diastolic hypertension. Since conventional renal function tests may be normal, diagnostic investigation should include aortogram, radioactive renogram, Howard test, and TEAC test.

In our series of 43 patients investigated, 14 have undergone operation, 7 are considered cured, 3 were inadequately followed, 2 are unchanged, and 2 have died.

Analysis of the diagnostic tests done in the 14 operated patients revealed the following: Aortograms were abnormal in all, with suggestive bilateral abnormality in 4. With the abnormal aortogram as a point of reference, the following results were obtained: (*a*) Intravenous pyelograms (14 patients) revealed concordant, significantly smaller renal shadows in 9. Estimated function was depressed concordantly in 5, equal in 8, and discordantly better in 1. (*b*) Radioactive renograms (14) were concordantly abnormal in 9, bilaterally abnormal in 2, and normal in 3. (*c*) Howard tests (12) revealed concordant abnormalities of water excretion in 10 and of sodium excretion in 3. Sodium determinations were unsatisfactory in 7. Results were normal in 2.

TEAC tests (9) disclosed pressor responses in 2.

From an analysis of the above diagnostic tests performed in those patients suffering from secondary hypertension who were cured or unchanged by surgery and in those with primary hypertension not operated on, we conclude that there is no single fully reliable screening test to detect which patients have surgically correctable renal hypertension. A plea is made for thorough investigation of each patient.

Evolution and Significance of the T-Wave Changes in the Normal Newborn During the First Three Days of Life (P)

Gershon Hait and Benjamin M. Gasul, Chicago, Illinois

The presence of positive T waves in right precordial leads and negative T waves in left precordial leads in the normal newborn has not been satisfactorily explained. In an attempt to throw some light on this phenomenon, 260 electrocardiograms in 20 normal newborn infants were obtained and grouped in 17 time intervals: 0 to 5, 15 to 30, 45 minutes, 1, 2 to 3, 4 to 6, 7 to 10, 11 to 14, 15 to 18, 19 to 24, 25 to 30, 31 to 36, 37 to 42, 43 to 48, 47 to 60, 61 to 72, and 168 hours following birth. Whereas the mean QRS vector in the frontal plane remained stable, a definite evolutionary pattern of T-wave changes occurred. This evolution, which to our knowledge has not been described previously, may be divided as follows:

In the first period (0 to 5 minutes), the mean T vector was located between +60 and −90 degrees in the frontal plane and between 0 and +90 degrees in the horizontal plane. T waves were positive in V_6 in 13 cases and isoelectric in 3 cases. No data were available in 4 cases.

In the second period (1 to 24 hours), the mean T vector rotated to the right and anteriorly in 19 cases. The mean T vector in the frontal plane traveled from 20 to 210 degrees and in the horizontal plane from 15 to 120 degrees. In 2 cases, in the horizontal plane no movement occurred. In lead I, T waves became negative in 8 cases and isoelectric in 12 cases. In the precordial leads, T wave in V_6 became negative in 10 cases, isoelectric in 9, and remained positive in 1 case, whereas in V_{3R}, the T wave became more positive than at birth in 13 cases.

In the third period (from end of second period to 7 days), the mean T vector reverted to the left in all cases and traveled anteriorly in 10 cases and posteriorly in 10 cases. By the time the mean T vector was completely restored, it was located in the horizontal plane between 0 to −60 degrees in all cases.

The findings seen at the end of the second period are suggestive of left ventricular strain. This might be a reflection of the work overload of the left ventricle which is markedly increased after birth.

Exercise Chest X-rays in Mitral Stenosis

Michael J. Halberstam, John S. Hanson, Burton S. Tabakin, and A. Bradley Soule, Burlington, Vermont

In mitral stenosis, the plain chest x-ray might be expected to change after exercise because of the characteristic rise in left atrial and pulmonary artery pressures with exercise in such patients, and likewise, a rough correlation might be expected between such pressures and size by x-ray. This theory has not been tested previously. Chest films were taken at rest and immediately after 3 minutes stair-walking in front of the x-ray cassette in 20 patients with mitral stenosis and 5 normal controls. Three radiologists separately

evaluated the paired, coded films without knowing which films were postexercise or if exercise had been performed at all.

Of the 60 readings on the 20 exercise patients, 37 were reported as showing increased vasculature in the postexercise films, 20 no change, and 3 increased vasculature in pre-exercise films. All radiologists gave similar reports of increased vasculature after exercise in 9 patients and were unanimous in finding no change in 3 others. In the remaining patients, there was some disagreement, with 1 radiologist usually finding minimal increase in the postexercise film. Of the 15 readings on the control subjects, 14 were reported no change.

Increased size of the main pulmonary artery, right and left pulmonary arteries, and the perihilar venous pattern were the most consistently noted changes. Changes in the size of the pulmonary artery segment could not be predicted from previously determined pressure changes, but definite changes in vascular size occurred only with significant mitral stenosis. This simple procedure deserves further attention in the clinical and research evaluation of mitral heart disease.

Use of Thrombectomy in the Treatment of Deep Thrombophlebitis of the Leg (P)

J. Alex Haller, Jr., Louisville, Kentucky

Acute iliofemoral venous thrombosis occurs most often in hospitalized patients and frequently follows abdominal operation and trauma. The much-feared complication of major pulmonary embolism is quite rare, but the usually overlooked complication of deep venous incompetence is common. The resulting postphlebitic limb probably constitutes the most serious consequence of the thrombosis. The high incidence of these debilitating sequelae in young adults indicates an urgent need for re-evaluation of current therapy.

None of the components of presently accepted therapy is directed toward prevention of the late complications by reconstituting normal venous flow. The prevention of valve incompetence can be accomplished only by eradication of the fresh thrombus. To this end a number of investigators are currently studying the effect of fibrinolytic agents.

Immediate removal of the venous thrombus constitutes a direct approach which has received less extensive clinical trial than seems indicated on the basis of our early results. The purpose of this paper is to describe our experience with thrombectomy for acute iliofemoral venous occlusion in 25 patients, the indications for operation, the technic employed, the role of venography in the diagnosis and follow-up of these patients, and the use of adjuvant anticoagulation.

Studies on the Mechanism of the Abnormal Sodium Excretion in Arterial Hypertension (P)

Irwin B. Hanenson, Edmond Ricanati, Nathan Polasky, and Benjamin F. Miller, Cincinnati, Ohio*

Hypertensive patients excrete an intravenous sodium load more rapidly than individuals with normal blood pressure. To obtain a better understanding of this abnormality, we have studied the relationship of sodium excretion to other closely associated aspects of renal function, such as diluting and concentrating ability. In patients with labile and uncomplicated essential hypertension, the effects of hydration and dehydration have been observed on the excretion of sodium, potassium, urea, water, and total osmoles.

The significant results were as follows: (1) Hydration in the hypertensive patients was associated with decreased ability to dilute urine. This was accompanied by increased urinary sodium concentration and excretion. Maximal diuresis and free water clearance remained normal. The antidiuretic response to exogenous pitressin was reduced. (2) Dehydration in these individuals was characterized by an impairment of urinary concentrating ability and by increases in both urine flow and sodium excretion. (3) In 3 labile and 5 essential hypertensives, the maximal tubular excretory capacity of para-aminohippurate was found to be the same as in the group of normal controls.

The results indicate that uncomplicated hypertensives have, in addition to the impairment of sodium excretion, defective diluting and concentrating capacities. These defects appear to be interrelated, suggesting a functional disorder of the countercurrent system in the renal medulla. Such a disturbance could result from the pressure-dependent nature of the blood flow through the vasa rectae.

Digitalis Tolerance in Dogs Following Extracorporeal Circulation

Masauki Hara, Ben M. Lincoln, William T. Dungan, G. Doyne Williams, and Raymond W. Browning, Little Rock, Arkansas

There is clinical evidence, incompletely documented, that following extracorporeal perfusion, patients are prone to develop digitalis toxicity on a conventional dosage schedule. This study was undertaken in an attempt to establish the digitalis tolerance of dogs following extracorporeal perfusion by determining toxic doses before and after perfusion using electrocardiographic criteria. Acetyl strophanthidin was administered to 17 dogs 2 to 3 hours after a 30-minute perfusion of 80 to 100 cc./Kg. which was acceptable by current clinical and laboratory standards. Six of the ani-

mals were cooled to 28 to 32 C. for 8 to 10 minutes. An average dose of 1.74 mg. was required for toxicity before bypass, compared to 0.72 mg. after perfusion, the latter being about 40 per cent of the control dosage. The results in the hypothermic group did not differ from the normothermic group. Twelve dogs were long-term survivors. Two animals died with electrocardiographically documented ventricular fibrillation following postperfusion digitalization, and the remaining 3 died of other causes. Toxicity studies in control animals before and after thoracotomy, 24 hours after cardiopulmonary bypass or hypothermia alone have not shown any appreciable variations. Serial serum potassium and calcium levels and blood pH in 8 experiments did not show any consistent deviations. Determinations of coronary sinus potassium in 10 additional experiments did not reveal any significant efflux from the myocardium following administration of toxic doses of acetyl strophanthidin; however, some animals manifested moderate hypopotassemia. Preliminary data from current studies probing the cause of the unexplained digitalis sensitivity suggest that the half-life of radioactive tritiated digoxin is prolonged after perfusion.

Chronic Pulmonary Artery Occlusion: Mediastinal Collagenosis and Other Conditions, with a Review of the Literature

James D. Hardy, Thomas R. Arlander, Thomas M. Blake, and Robert D. Sloan, Jackson, Mississippi

Chronic obstruction of the main trunk of the pulmonary artery or its larger branches extensive enough to produce significant circulatory embarrassment is an uncommon entity. Such obstructions may be due to a variety of pathologic processes, but in general, these fall into 2 groups. First, there are those lesions related primarily to the vessel lumen or wall, as exemplified by chronic pulmonary embolism or pulmonary artery thrombosis. Second, there are those lesions arising in the mediastinum or hilar areas which secondarily impinge on the lumen or involve the wall of the pulmonary artery or its major branches, such as occur in certain neoplastic or inflammatory processes.

Three cases have been used to illustrate some of the entities which may produce chronic obstruction of the pulmonary artery or its major branches. Case 1 was a 20-year-old girl admitted for severe pulmonary hemorrhage. Radiographs revealed apparent infiltrative changes at the base of the right lung. A systolic murmur was heard over this area. Bronchoscopy was negative. Angiocardiogram disclosed essentially complete occlusion of the left pulmonary artery, and differential bronchospirometry indicated minimal oxygen uptake on the left. At thoracotomy to free the left pulmonary artery of possible embolic or thrombotic occlusion, an exceedingly dense mediastinal and perivascular collagenosis was encountered. Following death early in the postoperative period, autopsy revealed massive mediastinal collagenosis with marked reduction of intraluminal diameter of both pulmonary arteries, more marked on the left. In case 2, chronic pulmonary embolism was present and in case 3, pulmonary artery thrombosis.

Prospective Study of the Physiologic Influences on Blood Pressure (P)

William R. Harlan, Durham, North Carolina, Robert Osborne, Boston, Massachusetts, and Ashton Graybiel, Pensacola, Florida

Recent concepts of the pathogenesis of hypertension view blood pressure as an inherited, graded characteristic responsive to physiologic influences, such as aging and weight. Data from a prospective study of 633 healthy men followed over a 19-year period have been analyzed and correlated with several physiologic parameters. Frequency distribution curves at 5-year intervals for systolic and diastolic blood pressure are similar to those presented by Pickering and demonstrate a definite skew toward higher diastolic pressures with increasing age. The group with casual blood pressures in the "hypertensive" range on follow-up study are composed of those individuals with the higher initial pressures and those with the greatest interval weight gain. Cold pressor tests performed on 273 members of the group on initial evaluation had no correlation with the development of subsequent elevated blood pressures. Somatotyping profiles were obtained initially and have been correlated with blood pressure. Observations have also been made on family history and blood lipids in this group. This study is felt to represent the only comprehensive long-term evaluation of the physiologic variables in blood pressure and to offer data pertinent to the pathogenesis of hypertension.

Dextrocardia: Analysis of 100 Cases and Family Study of Forty Cases

Lulu M. Haroutunian and Catherine A. Neill, Baltimore, Maryland

Among 100 patients attending the Harriet Lane Home Cardiac Clinic in whom the heart lay partially or totally in the right hemithorax, there were 23 cases of dextrocardia with situs inversus, 65 cases of isolated dextroversion of the heart, and 12 cases of dextroposition or single displacement

of the heart to the right. A detailed analysis was made of the clinical, radiologic, and electrocardiographic data in all cases; the cardiac diagnosis was based solely on these data in 27 and was confirmed by catheterization, angiocardiography, or surgery in 55 and on autopsy evidence in 18.

The following well-defined syndromes were encountered: (1) Ivemark's syndrome, i.e., splenic agenesis, partial situs inversus, and atrioventricularis communis (4 proved cases); dextroversion with single ventricle, transposition, and pulmonic stenosis (7 proved and 37 probable cases); (3) dextroposition with tetralogy of Fallot and absent sternum (3 cases); (4) dextroposition with hypoplastic right lung and anomalous venous return, "scimitar syndrome" (2 cases); (5) dextroversion with corrected transposition (2 cases); (6) dextrocardia or dextroversion with normal heart (6 cases).

Detailed analysis of the family history in 40 cases revealed 10 patients (25 per cent) who had a relative with congenital heart disease and 4 (10 per cent) who had a relative with dextrocardia; there was 1 consanguineous marriage.

Clinical and Hemodynamic Correlation in Recurrent Postoperative Mitral Valvular Disease (P)

Donald C. Harrison,† Lockhart B. McGuire, John W. Hyland, Florence W. Haynes, and Lewis Dexter, Boston, Massachusetts

Clinical evaluation of patients who develop cardiac symptoms several years after mitral valvuloplasty is more difficult and less reliable than evaluation of patients with mitral stenosis before surgery. The clinical findings prior to surgery are well correlated with hemodynamic and surgical observations. Following successful surgery, patients retain many of the clinical characteristics of their initial disease, even when other complications appear. In an attempt to clarify the problem of postoperative assessment, 50 preoperative cases of mitral valvular disease have been reviewed and compared with 52 patients who developed a return of cardiac symptoms 2 to 7 years after mitral valvuloplasty. All patients had a complete clinical evaluation by the same observer and cardiac catheterization. Correct clinical assessment was made in 47 of the 50 cases prior to valvuloplasty but in only 38 of the 52 cases after valvuloplasty.

Four distinct complications have been noted as causes of recurring disability: (1) recurrent mitral stenosis, (2) mitral regurgitation, (3) a mixed lesion characterized by significant regurgitation in the presence of some degree of mitral stenosis, and (4) the appearance of other types of heart disease, especially aortic valvular and coronary artery disease. The latter group has been omitted from this study.

Recurrent mitral stenosis was present in 22, predominant mitral regurgitation in 18, and a mixed lesion in 12. The inaccuracy of our clinical assessment postoperatively has made it mandatory to use cardiac catheterization in the evaluation of all patients developing disabling symptoms after mitral valvuloplasty.

Restoration of Sinus Rhythm in Dogs with Chronic Complete Heart Block by Electronic Autopacing

Edward Harvey and Edward W. Hawthorne, Washington, D. C.

The most physiologic correction for chronic complete heart block would be continuous ventricular pacing at the ambient sinus rhythm. Preliminary to the construction of a completely portable, solid state autopacer, we have built a mechanoelectronic device which produces pacing voltages at a rate governed by sinus rhythm with provision for control of the P wave to stimulus interval. Paired electrodes are implanted in the right atrium and at the base of the right ventricle. The voltage from the atrium and the stimulus to the ventricle are conducted in a retractable cable with a slip ring assembly to give the animal maximum freedom of movement. The atrial P-wave voltage is used to trigger a stimulus generator after a preset time. The stimulus thus produced is returned to the ventricle which contracts. Stopping the autopacer restores idioventricular rhythm. We have used this circuit to provide the means for comparing the left ventricular dimensional consequences to graded pressure work loads in intact, awake dogs with complete heart, both at the heart block rate and at sinus rhythm.

Enigma of Mild Pulmonary Stenosis

L. Julian Haywood, Ronald H. Selvester, and Donald E. Griggs, Los Angeles, California

Because isolated pulmonary stenosis was discovered in several patients in whom this was not the first clinical diagnosis, we have analyzed data in 55 consecutive cases proved by catheterization. The following were the major diagnoses rendered prior to catheterization: atrial septal defect 7, ventricular septal defect 3, ventricular septal defect plus pulmonary stenosis 4, cushion defect 1, mitral insufficiency 1, and atrial septal defect plus pulmonary stenosis 2. Pulmonary stenosis was mentioned in the differential diagnosis in 28 cases and patent ductus arteriosus in 7. The most common symptom was decreased exercise tolerance in 19 patients; dyspnea, syncope, increased respiratory in-

fections, cyanosis, chest pain, and fatigue each occurred in a small number of patients. All patients had a systolic murmur grade I to IV on a scale of VI. Nineteen patients had systolic thrills, P_2 was increased in 22, and a fixed split was heard in 3 patients. A systolic ejection sound was heard in 8 patients. Cardiac enlargement was noted in one-half of the patients and two-thirds had a dilated pulmonary artery on x-ray. Abnormal electrocardiograms or vectorcardiograms were recorded in 31 patients, the most frequent being right axis deviation in 20 and some degree of right ventricular hypertrophy in 22. The phonocardiogram recorded a systolic ejection sound in 18, narrow fixed splitting of P_2 in 9 patients, and partial reversal of splitting in 5 patients. At catheterization, mild stenosis was present in 18 (right ventricular pressure 20 to 40 mm. Hg, gradient 10 mm. or more across valve), moderate stenosis in 14, and severe in 7 patients. Diagnostic error was greatest in the mild group (60 per cent). The difficulty of making a diagnosis on the basis of clinical findings in these patients without hemodynamically significant disease needs emphasis.

Oral Magnesium: Absorption and Effects on Cholesterol Levels

L. Julian Haywood, Ronald H. Selvester, and Donald E. Griggs, Los Angeles, California

Recent reports by Hans Selye and others have demonstrated the protective effects of feeding oral magnesium to animals on atherogenic diets against the development of myocardial lesions and atheromatous deposits. A search of the literature revealed little information regarding the absorption, excretion, and effects on lipid levels of magnesium in man; a long-term study is in progress in our laboratory.

A short-term study was carried out on the serum and urine levels of magnesium and serum cholesterol following the ingestion of 3 componds of magnesium by healthy subjects on normal diets. (Five subjects received $MgCl_2$ in capsules, 4 received $MgSO_4$ in capsules, and 5 received $MgCl_2$ in enseals.) Control levels of serum and urinary magnesium and serum cholesterol were taken for 3 days. Subjects were then given a single dose of magnesium compound, and serial determinations of serum and urine magnesium and serum cholesterol were measured at intervals during the day. For the next 4 days, the subjects received 1 mEq./Kg. of the magnesium compound, and daily determinations were made as before in morning and evening specimens.

Magnesium chloride capsules produced a 3-fold increase in urinary excretory rates of magnesium and a definite increase in serum levels. $MgCl_2$ enseals in the same dosage produced a 2-fold increase in urinary levels and increased serum levels. $MgSO_4$ resulted in no increase in serum or urine levels; diarrhea and dehydration were common in this group. Serum cholesterol levels fluctuated in all 3 groups, without definitely lowered levels at the end of observation.

Clinical and Laboratory Experience with Open-Heart Surgery for Mitral Valve Disease

Louis R. Head, James M. Head, Bruce R. Bodell, and Jerome R. Head, Chicago, Illinois

For 6 months, open-heart technics have been used for certain types of mitral valve pathology. With the system devised by Dr. Earle B. Kay, open procedures have been performed on 10 patients. Mortality and morbidity figures have been identical to those of other groups. In no instance has the heart-lung machine produced difficulties. Seven patients with mitral stenosis alone, in whom simple closed commissurotomy could not be done because of calcification or fibrous union of leaflets, have undergone open procedures without mortality. Satisfactory valve openings were obtained in all cases. Three patients, in whom stenosis was associated with insufficiency and right heart failure, succumbed within 3 weeks of surgery. In none could satisfactory correction of the insufficiency be obtained. Annular plication, replacement of leaflet deficits, and posterior leaflets support have failed, in our hands, to be effective in obtaining competent valves. With this experience, increased efforts have been made in the laboratory to construct complete valvular replacements. With flexible weaving technics, woven Teflon and woven silk valves have been produced which closely approximate the size and shape of the normal mitral valve. Measured physical characteristics, flexibility, total valve weight, surface smoothness, and electrical conductivity differ widely from those of normal valve tissue. The reported discrepancy between dog and man with regard to clotting on valve prosthesis has led to the study of adult sheep as laboratory animals. Whereas similarities in cardiac output, total body weight, and blood viscosity have been beneficial in preparation for initial adult patient surgery, the high flow rates through prosthetic valve implants have not decreased clotting tendencies. A disproportionally small heart and the elevated fibrinogen levels found in sheep blood are contributing factors. Further work is required prior to the clinical use of woven mitral valve duplicates. Patients with proved mitral insufficiency, in most cases, should be operated on with a suitable valve prosthesis on hand.

Systolic Ejection Time in Myocardial Disease

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The systolic ejection time (ET) in nonvalvular myocardial disease was evaluated in patients with and without congestive heart failure (CFH). The ET was measured on a carotid pulse tracing taken by means of a surface pickup, and corrected ejection time (CET) was obtained by dividing ET by the square root of the cycle length. Twenty-five normal subjects and 36 patients with nonvalvular myocardial disease (31 with recent and old myocardial infarction) were studied. In normal subjects, the mean CET was 0.31 second (range 0.28 to 0.35). In 27 patients with myocardial disease but without CHF, the mean CET was 0.29 second (range 0.26 to 0.32). In 9 patients with myocardial disease complicated by CHF, a mean CET of 0.25 second (range 0.24 to 0.28) was seen. Differences were significant at the $p < .001$ level. Of patients without CHF, 3 of 5 with myocardial infarctions less than 1 month old and 3 of 32 with chronic coronary artery disease showed a CET below normal limits. Seven patients followed for a period of up to 21 weeks after a myocardial infarction showed progressive increases in CET with recovery. There were 5 deaths in the series, 4 of which occurred in patients presenting with CHF and a markedly shortened CET (0.24 second). Recent evidence that stroke volume and ejection time are directly related, both in normal subjects and patients with CHF, suggests that decreased stroke volume is the predominant factor causing decreased CET. Determination of the CET is a simple method for the evaluation of impaired cardiac function in patients with or without clinical evidence of CHF.

Serum Manganese Value in Myocardial Damage

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In the normal heart, manganese occurs in an average concentration of 1,800 μg. $\pm$ 110 μg./100 Gm. of dried tissue. In the normal human, serum manganese concentration is 1.2 μg./100 ml. Following an infarction, the myocardium loses roughly 60 per cent of its manganese content. At the same time, there is a concomitant rise of manganese in the serum.

In a study at the Los Angeles County Hospital, serial determination of serum manganese along with serum transaminase was done on 45 patients with acute myocardial infarction. The average serum manganese values for patients with myocardial infarction ranged from 2.0 μg. to 3.5 μg. Our results indicate that the serum manganese elevation occurs within 8 to 10 hours after myocardial infarction and remains elevated for as long as 5 to 6 days. Similar results were obtained in experimental coronary ligation in dogs. The height and duration of the rise in serum manganese in these dogs showed a rough parallel to the extent of the myocardial damage.

Comparison of serum manganese and transaminase levels showed a close correlation between the 2. Both serum manganese and transaminase were elevated in prolonged tachycardia and in certain inflammatory conditions of the pericardium and myocardium. In the absence of proved myocardial infarction, transaminase values were falsely elevated in cases of coronary insufficiency, hepatitis, pancreatitis, lung abscess, pulmonary infarction, and perforated peptic ulcers.

Hence, we feel that in a doubtful case of myocardial infarction, serum manganese is a reliable test to confirm the diagnosis. Our laboratory has developed an easy, reproducible colorimetric method for serum manganese determination.

Electron Microscopy of Purkinje Fibers and Ventricular Muscle of Dog Heart (P)

Lawrence Herman, Jackson H. Stuckey, and Brian F. Hoffman, Brooklyn, New York

The fine structure of Purkinje and ventricular fibers of dog heart has been studied with the electron microscope. The ultrastructure of Purkinje fibers in the canine false tendon closely resembles that seen in the ungulate heart, contrary to the statements of Muir and others. The canine false tendons contain large numbers of collagen fibrils which surround centrally placed Purkinje fibers. These Purkinje fibers are separated into cells by intercalated discs which differ in several respects from those of muscle. The Purkinje cell contains a large, centrally located, and irregularly shaped nucleus surrounded by extensive glycogen-containing areas. Small numbers of myofilaments are present and appear as wisps of bundles in the glycogen-containing areas; some myofilaments show banding. Small mitochondria are randomly distributed in the cytoplasm and are less numerous than in ventricular muscle.

The ventricular muscle contains an orderly array of myofilaments with the typical banding pattern. Myofibrils are greater in number than in Purkinje fibers. Conversely, glycogen-containing areas are reduced in amount and restricted to localized regions at either end of the elongated muscle cell nucleus. Profiles of endoplasmic reticulum are more frequent than in Purkinje cells and are located between adjacent myofibrils and myofilaments. Mitochondria are larger and more elongated and contain more cristae than in Purkinje cells.

To our knowledge, this is the first reported study of the electron microscopy of Purkinje fibers in the dog heart. Differences in fine structure of Purkinje and myocardial cells were studied in relation to specialization of function.

Electron Microscope Studies of Human and Dog Heart Biopsies

Helen Hift, William P. Young, Vincent L. Gott, and Charles W. Crumpton, Madison, Wisconsin

Within recent years, open-heart surgery has made available biopsy material from the hearts of patients undergoing operations for a variety of congenital and acquired defects. The way has thus been opened to seek answers to the following questions: Are certain types of heart disease associated with specific structural changes which may become detectable at the level of the electron microscope? Is the severity of the disease a contributing factor? Do the surgical procedures of cardiopulmonary bypass or cardiac arrest give rise to any reproducible alterations? How does the dog, the standard subject in cardiovascular experimentation, compare to the human?

With these questions in mind, ventricular or atrial biopsies were collected from patients at the time when cardiopulmonary bypass or cardiac arrest was initiated and, whenever possible, after normal coronary circulation had been restored. Similarly, samples were taken from dog hearts before and after periods of experimental anoxic arrest. The tissues were fixed, embedded, and sectioned in the usual manner and examined under the electron microscope.

The results to date indicate that the structural components and spatial relationships are preserved optimally at an osmolarity near 0.37 M. A consistent finding has been the small size of the human mitochondria as compared to the dog. All other morphologic components appear to be similar in the 2 species. Thus far, we have not observed any striking alterations associated with any of a variety of heart defects, nor do periods of cardiopulmonary bypass lasting up to 1 hour seem to bring about any readily discernible changes.

Comparison of Serum Lipid Levels in Patients with Cerebrovascular Disease and in Normal Subjects

Norio Higano, William D. Cohen, and Roger W. Robinson, Worcester, Massachusetts

Because of previously demonstrated correlations between coronary atherosclerosis and abnormal serum lipid levels in both men and women, an attempt was made to determine whether similar relationships occurred in patients with cerebrovascular disease (excluding hemorrhage) as compared with sex- and age-matched individuals without demonstrable vascular disease. In order to obtain 124 subjects in the latter group, more than 400 presumably healthy volunteers 40 to 90 years of age had to be examined. These were compared with 113 male and 137 female patients who had been hospitalized with an acute cerebral thrombosis. Although no difference of serum cholesterol was seen in the males, the female patients had higher levels than the normals ($p < .05$). However, serum phospholipids and resultant cholesterol/phospholipid ratios were variable. The β- to α-lipoprotein cholesterol ratios were worse (i.e., elevated) in both male and female patients than in the normals ($p < .05$) because of decreased α-lipoprotein cholesterol levels in both male and female patients and higher β-lipoprotein cholesterol levels in the female patients. These results suggest a relationship between abnormal lipid metabolism and the development of cerebrovascular disease similar to that seen in coronary atherosclerosis.

Evolution of Acyanotic Tetralogy from Interventricular Septal Defect

Florencio A. Hipona, Barry T. Held, and Richard H. Greenspan, New Haven, Connecticut

Three distinct pathways for the evolution of interventricular septal defects are now known; each has different diagnostic, therapeutic, and prognostic implications: (1) development of increased pulmonary arteriolar resistance leading to pulmonary hypertension, (2) development of infundibular pulmonic stenosis with right ventricular hypertrophy leading to balanced or right-to-left shunt, and (3) spontaneous functional closure of the interventricular septal defect with a return to normal hemodynamics.

The purpose of this report is to present a group of patients who have been followed, both clinically and roentgenologically, for periods of 3 to 9 years. Initially, all had typical clinical roentgenologic and catheterization findings of an interventricular septal defect with increased pulmonary blood flow. Subsequently, these patients developed infundibular pulmonic stenosis, and they became functionally indistinguishable from cases of acyanotic tetralogy of Fallot.

The anatomic changes resulting from this transformation were vividly recorded in the serial roentgenograms and, in fact, permitted reconstruction of the pathophysiology from observation of the specific roentgen changes. The changes occurring in this group of patients, in contrast to those in other patients with ventricular septal defects, have been tabulated.

Determination of Coronary Arterial Flow Requirements During Total Cardiac Bypass

Teruo Hirose, William M. Lemmon, and Charles P. Bailey, New York, New York

A study has been conducted to determine the myocardial requirements under normothermic and hypothermic conditions in normal and diseased hearts. This information is especially desirable in the surgical treatment of coronary arterial or aortic valve lesions where direct coronary cannulation and perfusion are necessary. The actual requirements have not been determined until now, and clinical experience in the past has been on an empiric basis.

These studies have been performed on normal dogs, on human material obtained at autopsy, and on diseased human hearts. The technic has consisted of collection of the flow from the superior and inferior vena cava with a pulmonary artery clamp being applied while the coronary sinus returned, and all right-sided flow is collected. Thereby, all coronary flow except the left ventricular Thebesian flow is collected and accurately measured for given conditions.

To date, human application of these determinations has not been attempted, but in our experimental work coronary flow has been related to heart weight and subject size.

Mebutamate, a New Approach to the Treatment of Hypertension

L. Floyd Hobbs, Alexandria, Virginia

Either mebutamate (300-mg. tablets) or a mebutamate (300 mg.)-hydrochlorothiazide (25 mg.) combination was prescribed for 70 hypertensive patients. Choice and amount prescribed were based on the individual requirements and were adjusted accordingly. Eighty-nine per cent of the patients obtained a reduction in systolic or diastolic pressure or both. Reductions were gradual and continuous, with the greatest reduction usually occurring within the first 2 weeks. Some patients, especially older ones, were extremely responsive to the drug, and it was possible to reduce dosage and still maintain adequate blood pressure reduction. Edema, present in 46 patients before therapy, was eliminated in 33, reduced in 8, and unchanged in 5. Side-effects, predominantly drowsiness, were usually mild and, in most instances, could be eliminated by reducing dosage. It also was possible to reduce the dosage to eliminate side-effects and then to return to the initial dosage without the recurrence of side-effects. Since it was deemed unwise to risk blood pressure elevation by discontinuing previous therapy for several weeks before institution of present therapy, it was difficult to determine whether some of the side-effects were related to the dose level of mebutamate or to overlapping effects of previous and present medication. Of 25 patients who were improved or slightly improved on previous therapy, 19 obtained further improvement, and 6 maintained previous improvement. Of 22 who were not improved on all forms of previous antihypertensive therapy, 17 were improved, 3 were slightly improved, and 2 were not improved. The action of this drug is on the central nervous system. Because of its short duration of action, it is imperative that the patients take their medication on the prescribed schedule in order to maintain adequate and continuous reductions in blood pressure.

Refractoriness of the in Situ Conduction System of the Canine Heart

Brian F. Hoffman, Rudolf Th. van Dam, and Jackson H. Stuckey, Brooklyn, New York

During perfusion with total cardiopulmonary bypass, electrodes were placed on the right atrium, bundle of His, both bundle branches, Purkinje-papillary junctions (PPJ), and ventricular surfaces. At each site, strength-interval curves for unipolar cathodal stimulation were determined and bipolar leads recorded in order to determine the spread through the conduction system of premature beats evoked at various intervals of the cardiac cycle by stimulation at the above-mentioned sites. In the different parts of the conduction system below the AV node, the recovery of excitability and of conduction followed approximately the same sequence as the activation. The refractoriness of the PPJ outlasted that of its Purkinje fiber by about 20 msec. In the ventricular myocardium, the refractory period was approximately 50 msec. shorter than in the conduction system. After early stimulation, local delays of about 50 msec. were observed in the appearance of the action potentials. The early action potentials often displayed marked notching, both near the stimulus site and at a distance, indicating conduction in refractory fibers. During the last third of the refractory period, conduction velocity depended on differences in recovery between the various structures. Conduction was very slow in a downward direction, toward still refractory parts, and much faster toward regions of the conduction system which had already recovered. All extrasystoles originating in the ventricular myocardium entered the conduction system, the pathway of entry depending on the conditions of refractoriness and sometimes involving relatively long detours instead of the shortest anatomic pathway.

Utility of RISA Blood Volumes in Total Cardiopulmonary Bypass in Dogs

Robert P. Hohf and Richard Goldman, Evanston, Illinois

During total cardiopulmonary bypass, hypovolemia may result from surgical blood loss, or hypervolemia may be produced by transfusion to maintain a high flow rate. Despite attempts to maintain normovolemia by estimation of blood loss and machine blood volume, a problem exists in assuring a normal corporeal blood volume after perfusion.

In 15 dogs weighing 12 to 20 Kg., blood volumes were determined with RISA immediately before and after total body perfusion. Despite careful estimation of blood loss and corresponding replacement, 11 animals had a deficit and 4 an excess. The range was −39.8 cc./Kg. to +12 cc./Kg. with a median of −15.9 cc./Kg. The absolute blood volume changes were −470 cc. to +180 cc. with a median of −260 cc.

The postperfusion blood was useful also in calculation of the heparin still present. This made possible a more accurate dosage of polybrene or protamine as antiheparin agents. Both may have an anticoagulant action if used in excess. The ratio of the minimum dose of polybrene to heparin was 0.5 to 1, and for protamine it was 1 to 1.

Measuring blood volumes with RISA before and after total body perfusions is a relatively simple, direct method that permits corrections of corporeal blood volumes with increased accuracy. In addition, it makes possible administration of antiheparin agents.

Influence of Temperature, K^+, and Ca^{++}, on the Effect of Ouabain on Ca^{45} Entry and Resting and Contractile Tension in Rabbit Atria (P)

William C. Holland, Jackson, Mississippi

In K-deficient media (1.35 mM), ouabain (10^{-6} M) increased resting tension (contracture) 1.5-fold and Ca inflow 2-fold, respectively, over a 30-minute interval in atria stimulated 180 c.p.s. at 30 C. No changes were observed in quiescent preparations. An increase of K (108 mM) or a decrease of Ca (0.14 mM) prevented the above-described changes. Q_{10} values for the action of ouabain on resting tension and Ca inflow varied between 3.5 and 4.2. If the K concentration was maintained at 5.4 mM and Ca reduced to 0.81 mM, ouabain was found to increase contractile tension 1.6-fold and Ca inflow 1.4-fold, respectively, at 30 C. No changes in resting tension were noted. Further study revealed that the Ca^{++}/K^+ in the media determined whether ouabain increased contractile tension or produced contracture. In general, if the ratio exceeded 0.6, ouabain induced contracture; at values between 0.1 and 0.6, ouabain increased contractile tension only. At values below 0.01, all actions of ouabain were abolished. Changes in contractile and resting tension were always accompanied by an increased Ca inflow. However, the effects on Ca entry were considerably greater when ouabain produced contracture. From these studies, it was concluded that ouabain produced its effects by acting on some Ca-dependent reaction(s) in the excitation-contraction coupling mechanism in the myocardium.

Incorporation of Radiosulfate into the Aorta of Human Subjects

William Hollander, Aram V. Chobanian, Melvin H. Farmelant, and Belton A. Burrows, Boston, Massachusetts

Previous studies have indicated that the uptake of radiosulfate by a tissue is a measurement of chondroitin sulfate formation. To determine whether an alteration in mucopolysaccharide metabolism might exist in atherosclerosis, the rate of incorporation of $S^{35}O_4$ into the human aorta with and without atherosclerosis was studied. $Na_2S^{35}O_4$ in a dose of 200 to 600 mc. was injected intravenously into terminally ill patients with malignancy, hypertension, congestive heart failure, and cirrhosis. From 4 hours to 9 days after the injection, their tissues were obtained at autopsy and analyzed for radiosulfate activity. Electrophoretic studies of the aortic tissue revealed the presence of radioactivity in a metachromatic staining substance which had the same electrophoretic mobility and staining characteristics as chondroitin sulfate.

The radiosulfate concentration (per cent dose/Gm. dry tissue) in 6 of 10 atherosclerotic plaques was increased by 39 to 127 per cent (average 72 per cent) as compared to that of the adjoining normal appearing intima. In the 4 other plaques, 2 of which were notably hard and calcified, the radiosulfate content was less than that of the adjoining normal intima by 22 to 63 per cent (average 53 per cent). Histologic studies suggest that the degree of cellularity and fibrosis of the atherosclerotic lesion may influence the radiosulfate uptake.

In conclusion, the incorporation of radiosulfate into the human aorta appears to be an index of chondroitin sulfate formation which may be altered in atherosclerosis.

Quantitative Assessment of the Mechanical Function of the Heart by Ultralow-Frequency Ballistocardiography

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The use of weakly damped, ultralow-frequency ballistic platforms with an acceleration transducer allows determination of the body-platform acceleration due to systolic ejection and blood flow in great vessels. The average mean values for the I-J stroke from a pendulum (49 subjects; 4.90 ± 1.17 cm./sec.^{2}), ball-bearing bed (46 subjects; 4.43 ± 0.95 cm./sec.^{2}), and an ultralow-frequency spring bed (25 subjects; 4.04 ± 0.94 cm./sec.^{2}) have been determined and related to the value given by Scarborough from a differential pendulum (25 subjects; 5.81 ± 0.91 cm./sec.^{2}).

The calculated average mean I-J stroke force ($F = M \cdot A/G$) values for the pendulum (434.15 ± 95.3 Gm.), ball-bearing bed (395.66 ± 91.5 Gm.), and the spring bed (405.98 ± 87.3 Gm.) were compared to the values given by Scarborough for a differential pendulum (485.8 ± 82.9 Gm.), Von Wittern for a simple pendulum (4 subjects, 365 Gm.), and Starr's value for a high-frequency spring bed (413 Gm.).

These studies indicate that the differential pendulum is the most sensitive of the systems described to date for study of the acceleration ultralow-frequency ballistocardiogram. The reasonable closeness of values from different ultralow-frequency systems supports the opinion that the ultralow-frequency technic is suitable for assessing quantitatively the higher dynamic aspects of cardiac function. Determination of normal values for males and females of different age groups will permit the use of this technic in studying the dynamic aspects of cardiac function in abnormal subjects.

Direct Cardiac Effects of Dopamine and Tyramine (P)

John C. Holmes and Noble O. Fowler, Cincinnati, Ohio

Dopamine (3 hydroxytyramine), a precursor of norepinephrine and epinephrine, has been shown to increase cardiac output of human subjects. The purpose of the present study was to determine the inotropic and chronotropic effects of dopamine and tyramine in the dog heart-lung preparation. These effects were recorded by a strain gauge arch sutured to the right ventricle.

With the cardiac rate held constant, dopamine (25 to 1,500 μg.) increased the cardiac output 53 to 121 per cent, contractile force 8 to 192 per cent, and blood pressure 12 to 31 per cent above control levels. Norepinephrine (2.5 to 20.0 μg.) subsequently given to this series increased cardiac output 42 to 228 per cent, contractile force 67 to 179 per cent, and blood pressure 7 to 40 per cent. In each animal, a prompt decrease in right and left atrial pressures occurred with both sympathomimetic amines. In uncontrolled rate preparations, these 2 drugs also produced significant increases in heart rate.

In other animals, tyramine was studied in amounts of 25 to 250 μg. At a dose of 250 μg., there was consistent increase of cardiac output (40 per cent average), ventricular force (47.5 per cent average), and blood pressure (12.5 per cent average) and decrease of right atrial pressure (38 per cent average) and left atrial pressure (35.5 per cent average).

It is concluded that dopamine has a significant positive inotropic and chronotropic cardiac effect over the dosage range studied. Tyramine has similar inotropic effects; its chronotropic action has not been studied.

Induction Pacemaker for Complete Heart Block

George R. Holswade and Constantine Linardos, New York, New York

The induction pacemaker developed for this study consists of a receiving coil, a transmitting coil, and a control unit. The 3-by-5-mm., Silastic-coated receiving coil, 8 cm. in diameter, is implanted in the subcutaneous tissue, and 2 wire electrodes extend to the myocardium. A lightly padded transmitting coil of corresponding size is placed on the skin overlying the receiving coil. A small cable connects the transmitting coil and the control unit. The original power and control unit was a bedside model operating on 110 volts. Through it, the amplitude and frequency of the pulses can be varied. A portable control unit, measuring 6 by 6 by 1½ inches, with a battery life of 400 hours has been developed.

Complete heart block was produced surgically in 37 dogs, and receiving coils with myocardial electrodes were implanted in 31 animals who survived. In each case, the heart could be paced perfectly immediately after the implantation. Since it was not practical to pace the dogs continuously, the mortality due to heart failure with ascites and pneumonia was high. The longest survivors so far with functioning coils have been 2½ and 3 months. Receiving coil failure occurred twice. Various types of myocardial electrodes have been tried in an effort to decrease myocardial fibrosis at the electrodes and breakage of electrode wires.

The chief advantages of the induction pacemaker over a completely implantable pacemaker is the ability to vary the heart rate, depending on the clinical needs of the patient, and easy accessibility for battery changes.

Utilization of the Atrial Appendages for Extracardiac Shunting Procedures

George R. Holswade, Constantine Linardos, and Mary Allen Engle, New York, New York

The atrial appendage has served the surgeon well in many procedures on the heart. Perhaps its greatest use has been as a means of easy entry for the exploring finger in the performance of mitral valvulotomy and for the introduction of drainage catheters for cardiac bypass. Procedures in which the atrial appendage has been anastomosed to another vessel have not been satisfactory for clinical use in most cases.

In an effort to increase the usefulness of the atrial appendage, shunting procedures involving the atrial appendage were performed in 54 dogs and the results studied. Extracardiac anastomosis between the 2 atrial appendages was performed in 36 animals by 2 different routes. When this was done through the transverse sinus posterior to the great vessels, thrombosis invariably occurred, regardless of whether a prosthesis or anticoagulants were used. Anastomosis of the 2 atrial appendages anterior to the great vessels provided a shunt which remained open in most animals. It is believed that an extracardiac connection between the 2 atria may have a useful application as the first stage of a 2-stage procedure for correction of transposition of the great vessels.

Right atrial appendage to pulmonary artery anastomoses tended to remain open, and when the tricuspid valve was obstructed by sutures, the right atrial to pulmonary artery shunt functioned well in approximately three-fourths of the animals.

Cardiac Effects of Acute Occlusion of the Aorta

Robert W. Hopkins, Fiorindo A. Simeone, and Otto Haiderer, Cleveland, Ohio

Effects of acute occlusion of the thoracic aorta on cardiac function were observed in 60 mongrel dogs under pentobarbital anesthesia.

The cardiac output was estimated by the dye-dilution technic, and the cardiac and stroke indices were calculated. A bonded arch strain gauge was sutured to the left ventricle to record myocardial contractile force. Changes in available oxygen were determined by means of a platinum microelectrode polarograph. Carotid and femoral arterial pressures, right and left atrial pressures, and electrocardiograms were recorded.

With aortic occlusion, a prompt and sustained increase in proximal arterial pressure and a decrease in pulse rate occurred. Stroke index showed little change, while the cardiac index decreased significantly in most animals. The left ventricular work per stroke increased, although the amount of work done by the left ventricle per unit of time tended to be unchanged during the period of occlusion. Myocardial oxygen showed a reproducible decrease in 31 tracings, a rise in 15, and no significant change in 20. No serious cardiac arrhythmias were observed, and no animal died during the period of observation.

Occlusion of the abdominal aorta just above the trifurcation led to little change in the observed parameters.

These data suggest that the heart in dogs compensates satisfactorily for the increased load provided by acute obstruction to the thoracic aorta.

Effect of Spatial Orientation on the Septal Contribution to the Early QRS Complex (P)

Leo G. Horan, Memphis, Tennessee, and Fred L. Hansen, New Orleans, Louisiana

Exact anatomic orientation of the heart was compared with apparent direction of electrical activity during the QRS complex in 2 groups of dogs.

In group I, spatial orientation of selected instants of the early QRS complex (e.g., 10 msec. after onset) was determined for McFee-Johnston vectorcardiograms and defined in spheric coordinates. Measurements of size and orientation of the right and left septal surfaces in serial frozen sections of the thorax were translated into vector quantities. The limits of variation of orientation of early QRS were greater than the limits of variation for anatomic orientation but were still relatively restricted.

In group II, components of early QRS attributed to each ventricular free-wall were identified during the transient instillation of intracavitary CO_2 in the opposite chamber. Septal components were then determined by vectorially subtracting both free-wall components from the pregas control vectors at each instant. Rotation of the heart in the closed chest was then usually performed by means of previously placed guy-sutures. The septal electrical vector 10 msec. after the onset of ventricular excitation was found to be oriented very nearly parallel to the respective septal anatomic vectors in all animals, with or without rotation of the heart.

These results support the concept that the surface report of septal electrical activity is severely regimented by the shunting effect of the blood masses and, therefore, largely dependent on anatomic orientation of the septum.

Possible Hemodynamic Basis for Beneficial Effects of a Monoamine Oxidase Inhibitor in Angina Pectoris

David Horwitz, Leon I. Goldberg, and Albert Sjoerdsma, Bethesda, Maryland

Monoamine oxidase inhibitors have been reported to be effective agents in the therapy of angina pectoris. In this study, changes in heart rate and blood pressure in response to moderate, standard-

ized treadmill exercise were determined in 3 patients with angina pectoris. After 6 to 8 weeks of control observations (2 to 5 times/week), during which the patient received a placebo, isocarboxazid was administered in doses of 20 to 50 mg./day, and exercise tests were continued. Maximum heart rate and blood pressure during exercise were significantly reduced ($p = <.01$) in each patient after 2 to 3 weeks of inhibitor therapy. A decrease of angina accompanied the diminished cardiovascular response in each subject and was most marked in 1 patient with labile hypertension whose exercise time without angina was more than doubled after therapy. In this patient, the blood pressure after 7 minutes of exercise was reduced from an average of 199/137 mm. Hg before therapy to 149/103 mm. Hg after therapy, and heart rate was reduced from an average of 109 beats/min. to 90 beats/min. After discontinuation of isocarboxazid, responses to exercise returned toward pretreatment values in each patient. These studies suggest that attenuation of hemodynamic responses to exercise by monoamine oxidase inhibitors may be responsible for whatever effectiveness they may have in therapy and provide a more rational basis for selection and treatment of such patients.

Increased Resistance to Fibrinolysin as Measured by Thrombelastography Following Treatment (P)

Orville Horwitz, David Devon, Brooke Roberts, and Howard M. Rawnsley, Philadelphia, Pennsylvania

Six patients suffering from thromboembolic phenomena were treated with fibrinolysin in dosages of 200,000 to 400,000 units. Before treatment was started, thrombelastographic studies were performed to determine the concentration of fibrinolysin necessary to prevent clot formation. A concentration of 25 units/ml. of blood in the cuvette of the thrombelastograph effectively prevented clot formation in all cases. Within 10 days after an injection of fibrinolysin, a concentration of at least 400 units/ml. of blood was invariably necessary to prevent thrombus formation. Six other patients, also suffering from thromboembolic diseases but not treated with fibrinolysin, who were similarly tested, showed no such changes. The resistance to thrombolysis, measured by the thrombelastogram, had then increased by 1,500 per cent as a result of treatment with fibrinolysin.

Protein electrophoretic patterns and immunologic studies were performed simultaneously with the thrombelastographic determinations.

The combined studies strongly suggest an antibody reaction to fibrinolysin as a result of even short-term therapy.

Validation of Palpation of the Cardiac Apex Impulse as an Index of Left Ventricular Hypertrophy

Charles R. Howie, Mary Ellen Clifford, Delbert E. Boblitt, and Park W. Willis, III, Ann Arbor, Michigan

Forty-six hypertensive and 15 normal subjects were studied by palpation of the cardiac apex impulse, chest x-ray, electrocardiogram, and ultralow-frequency displacement records of the apex impulse. X-ray evaluation included cardiothoracic ratio measurements, determination of heart size with reference to the tables of Ungerleider and Clark, and appraisal of the plain films by a roentgenologist experienced in cardiac examination. The most distinctive characteristic of the hypertensive group by low-frequency record was prolongation of the apical systolic outward movement above the diastolic baseline.

X-ray evidence of left ventricular hypertrophy was found in 28 hypertensives (61 per cent); electrocardiograms fulfilling at least one criterion of left ventricular hypertrophy were recorded in 27 (59 per cent), and ultralow-frequency records revealed apical systolic out-thrust duration greater than normal (0.14 second) in 34 (74 per cent). Thirty-four of 46 hypertensives had evidence of left ventricular abnormality by at least 2 methods of study. Comparison of the results of palpation (46 hypertensive and 15 normal subjects) with ultralow-frequency records revealed agreement in 50 subjects (81 per cent). By palpation, the apex impulse was normal in 20 of 25 subjects with measured duration under 0.14 second and prolonged in 31 of 36 subjects with measured duration over 0.14 second.

The ultralow-frequency record is apparently the most sensitive single index of left ventricular abnormality in hypertension. Estimation of the duration of the apex impulse by palpation is a convenient and reasonably accurate substitute for low-frequency records.

Acquired Aortic Stenosis

Charles A. Hufnagel and Peter W. Conrad, Washington, D. C.

A technic for the approach to the aortic valve and aortic root by the production of cardiac arrest using local cardiac cooling has been developed and clinically applied to the surgical correction of aortic stenosis. The variety of pathologic forms seen at operation include (1) commissural fusion, fibrous or calcific, (2) calcification of leaflets, (3) supravalvular bridging of leaflets, (4) subvalvular calcification, (5) leaflet fusion, (6) calcification and/or fibrosis with inadequate valve closure, and (7) combinations of above.

Direct reconstruction of the valve by decalcification, commissural incision, and removal of bridges and mechanical barriers to satisfactory valve function can be achieved in many valves. These measures do not entirely eliminate the possibilities of recurrence of stenosis.

Of 34 patients with calcific aortic stenosis, adequate valve reconstruction could not be achieved in all by the above methods, and excision of part or all of the valve was necessary to produce a satisfactory, functional valve. Five had total valve replacement, and 6 had 1 or 2 prosthetic cusps inserted.

These experiences lead us to conclude that partial or total valve replacement must be available when a surgical approach is made to correct aortic stenosis and that replacement of all or part of the aortic valve is desirable in an increasingly large group of patients. The present methods, using prostheses, make possible the restoration of valve orifices without significant gradients and without regurgitation.

Direct Treatment of Aortic Regurgitation (P)

Charles A. Hufnagel and Peter W. Conrad, Washington, D. C.

The study of 150 patients who had direct correction of aortic insufficiency showed diverse anatomic lesions which included (1) dilatation of the aortic root, (2) aneurysm of the sinus of Valsalva, (3) dissecting aneurysm, (4) prolapse of cusps, (5) perforation of cusps, (6) contraction of cusps, and (7) rupture of cusps.

The methods used for the repair have been individualized to meet the requirements of these varied pathologic problems and have included bicuspidization with excision of the noncoronary cusp, resection of the ascending aorta with and without bicuspidization, resection of aneurysms of the sinus of Valsalva, direct leaflet repair, leaflet suspension, and replacement of 1 or more cusps with prosthetic leaflets, including total valve replacement. During the past 18 months, almost all lesions with leaflet damage have been treated by leaflet replacement or valve replacement. In cases where reconstruction of valve substance was accomplished without prostheses, there have been recurrences of aortic leakage due to breakdown of the remaining valve tissue months after operation. Prostheses for replacement of 1 or more leaflets have been used in 75 patients. Total valve replacement has been accomplished in 24 patients with 17 survivors with good results. Total valve replacement has been used in the group with severe disease and has been associated with a higher risk than in less advanced patients who required 1 or 2 cusps to achieve correction. Improvement in valve prostheses has now made possible application of this technic to less advanced patients where risk is markedly decreased.

Comparison of Continuous Long-term Heparin and Oral Anticoagulation in Clinical Coronary Atherosclerosis

Leo Hughes, Seattle, Washington, Frede Mortensen, St. Louis, Missouri, and Leela Shourie, Bombay, India

A total of 104 patients with severe (grade III to IV) angina pectoris and 1 or 2 previous "poor-risk" myocardial infarctions were placed in 2 matched groups and treated continuously with anticoagulants for 24 months or until withdrawal by death or complication. There were 2,299 months of therapy, or an average of 22 months per patient. Concentrated aqueous heparin in doses of 100 to 200 mg. was given subcutaneously every 12 hours in 53 patients, while 51 patients received warfarin orally.

Heparin patients had 3 deaths (5.6 per cent) and 6 recurrent infarctions (11.0 per cent), in contrast to 8 deaths (16.7 per cent) and 14 recurrences (27.5 per cent) in the oral anticoagulant group. Definite, progressive improvement occurred in the anginal syndrome in 43 patients (81 per cent) receiving heparin and in 25 patients (49 per cent) on oral therapy. The degree of improvement was strikingly greater with heparin. Decreased nitroglycerin consumption paralleled these results quantitatively. More frequent favorable changes in interval electrocardiograms and ballistocardiograms of the heparin group provided objective evidence that corresponded closely with the subjective benefits in angina pectoris. Total serum cholesterol decreased more than 40 mg. per cent in 31 heparin patients. No similar cholesterol reduction occurred with oral therapy.

The length of observation was adequate to obtain sufficient patient months on anticoagulant therapy to demonstrate the superior effects of heparin. These results indicate that continuous long-term anticoagulation with heparin is feasible, safe, and highly beneficial in the therapy of clinically severe, advanced coronary atherosclerosis.

Right Ventricular Hypertrophy at High Altitudes (P)

Herbert N. Hultgren and Harry A. Miller, Palo Alto, California

Little information is available regarding the incidence and degree of hypertrophy of the right ventricle in humans and animals living at high altitudes. Since the relative weight of the right ventricle is proportional to the pulmonary artery

pressure, such data would provide indirect evidence of the effect of chronic hypoxia on the pulmonary circulation.

For these reasons, studies have been made of the weight of the right ventricle in formalin-fixed hearts obtained at autopsy from 11 infants (age 1 to 16 weeks) and 6 different animal species residing at altitudes between 12,500 and 14,200 ft. in the central Peruvian Andes.

After removing nonventricular structures, the free walls of the right and left ventricles were dissected away from the septum and each of the 3 portions weighed separately. Identical studies were made of similar numbers of hearts obtained from animals and humans at sea level.

The mean right ventricular weights, expressed as a percentage of total ventricular weight, in the hearts obtained at high altitude are summarized below (the mean control sea level values are given in parentheses): eleven infants 32.7 (29.7), 10 steers 25.8 (22.1), 20 lambs 26.3 (21.6), 12 pigs 26.7 (23.2), 5 dogs 29.2 (24.4), 10 rabbits 30.9 (22.7), 10 guinea pigs 26.7 (20.4).

These data indicate that in human infants and various animal species living at high altitude, there is a moderate degree of right ventricular hypertrophy which is compatible with a moderate elevation of pulmonary artery pressure, probably mediated by chronic hypoxia. Only slight species differences are apparent in the groups studied, but all of the species studied were tolerant and acclimatized to life at high altitude.

Effect of Employment on Heart Disease

Camp S. Huntington, Bartlesville, Oklahoma, and W. Best Thompson, Oklahoma City, Oklahoma

A total of 432 employees of the Phillips Petroleum Company with definite cardiovascular disease have been observed over a 5-year period to determine the effect of employment on heart disease.

There are 242 patients currently employed. Of 208 employees with known coronary artery disease, 68.5 per cent were still employed at the conclusion of the observation or had worked until normal retirement had taken place. In 26.1 per cent, there were either cardiovascular deaths, medical retirements, or termination.

A greater incidence of hypertensive cardiovascular disease was observed in white collar workers until the age of 60. At the end of the observation period, 73 per cent of the hypertensive employees were still employed or had gone on normal retirement.

Final evaluation of 41 rheumatic heart disease employees revealed that in only 12 per cent had there been either cardiovascular termination or cardiac death. This study would indicate that the employment of the rheumatic heart patient should be at the white collar level.

The most death-dealing combination from the cardiovascular standpoint appeared to be coronary artery disease, hypertension, and obesity, which accounted for 26 per cent of the deaths. Of the coronary group deaths, 11.5 per cent occurred on the job. None of these, however, was associated with unusual stress or strain. In 29.4 per cent, work performance was valued at a "premium" level.

In summary, there was no evidence of adverse effect on the natural course of heart disease in the working cardiac when he was correctly placed according to his capacity and with adequate medical attention. Increased mortality and poor work performances are not the outcome of the employment of the cardiac patient.

Response of the Arterial Wall to Localized Chronic Hypotension

Elias A. Husni, Cleveland, Ohio, and William C. Manion, Washington, D. C.

These experiments were undertaken to study the effect of chronic arterial hypotension on the local arterial smooth muscle. Chronic hypotension was produced in the arterial tree of 1 hind limb in 18 adult dogs by inducing a thrombotic occlusion in the common femoral artery. The contralateral artery served as control. The intravascular pressure was measured at weekly intervals in the popliteal arteries. Paired segments from the right and the left popliteal arteries were obtained from each animal for histologic studies and for dry weight and total nitrogen determinations.

The popliteal artery distal to the occlusion was remarkably small and thin compared to its control. The intravascular pressure here was 15 to 55 mm. Hg (8 to 30 per cent) lower than the control. Histologic examination revealed remarkable thinning of the media in the arterial tree subjected to the reduced intravascular pressure. This change was observed in all dogs and varied according to the severity and duration of the hypotension. The mean diameter of the media was 0.06 mm. (60 per cent) thinner, and its cross-sectional area was 0.4863 mm.^{2} (40.5 per cent) smaller than that on the control side. The results for dry weight and total nitrogen were commensurate with the histologic findings. The means for these variables were 7.5 mg. and 1.0 mg., respectively, for the hypotensive side and 8.7 mg. and 1.5 mg. for the contralateral control side.

These findings are consistent with atrophy of the media in arteries subjected to reduced intravascular pressure of long standing.

Left Atrial Angiocardiography in Left Atrial Thrombosis

John H. Huston, Milwaukee, Wisconsin

Clinical evaluation alone is sufficient for confident "closed" mitral valvulotomy in many patients. However, an unexpected large left atrial thrombus occasionally blocks the "closed" surgical approach to the mitral valve, necessitating a poorly tolerated retreat. It would seem desirable to detect such left atrial thrombi preoperatively.

In the presence of low cardiac output with severe pulmonary vascular disease, only selective injection of radiopaque material into the left atrium has given consistently satisfactory x-ray visualization. Left atrial catheterization is performed via the right saphenous vein, puncturing the interatrial septum by the Ross-Braunwald technic. While the transseptal needle is held immobile, its catheter is advanced until the tip also lies within the left atrial cavity. Manual injection of 30 cc. of radiopaque material through this catheter affords excellent left atrial opacification, with clear-cut filling defects when gross left atrial thrombi are present. Although 12 AP roentgenograms at 0.5-second intervals are usually taken, the single film exposed 1 second after completing the injection has invariably been diagnostic.

Five instances of gross left atrial thrombosis have been demonstrated in our last 13 consecutive patients with moderate-to-severe mitral stenosis (functional classification grade III). One left atrial myxoma was also discovered. In our experience, left atrial puncture has been technically easy, safe, and painless. Patient hazard and discomfort are only those associated with the injection of radiocontrast media.

We feel that left atrial angiocardiography is a valuable procedure in the consideration of "open versus closed" surgical correction of mitral stenosis.

Diuretic and Antihypertensive Properties of a Series of Benzothiadiazines in Hypertensive Cardiovascular Disease (P)

Duncan E. Hutcheon, Mortimer L. Schwartz, and Donna K. Rowland, Jersey City, New Jersey

The natriuretic and antihypertensive properties of several benzothiadiazines substituted in the 2, 3, and 6 positions were compared. The compounds included hydrochlorothiazide, the 3-dichlormethyl derivative (trichlormethiazide), and the 2-methyl-3-trifluoroethylthiomethyl derivative (polythiazide). Cases of hypertensive cardiovascular disease on a controlled diet of 18 mEq. sodium and 43 mEq. potassium per 24 hours were studied. Hypotensive responses were correlated with changes in 24-hour endogenous creatinine clearance, osmolal and solute-free water clearance, as well as sodium balance. The decrease in arterial blood pressure noted during thiazide therapy did not always parallel the increase in urine osmolality and sodium excretion, and the reduction in blood pressure was not accompanied by a natriuretic response in some cases on benzothiadiazine therapy. The results indicated there may be 2 mechanisms responsible for the antihypertensive action of the substituted benzothiadiazines: (1) The reduction in blood pressure produced by these drugs may be secondary to an increase in renal sodium excretion and a consequent negative sodium balance, and (2) in some cases, the substituted benzothiadiazines may have a primary vascular action which is responsible for the reduction in peripheral arteriolar resistance and fall in systemic arterial blood pressure observed during the administration of these drugs. This latter hypotensive mechanism appeared to be independent of the effects of these drugs on renal sodium excretion.

Clinical Application of Radiotelemetry in Man: Continuous Recording of Heart Rate

Gordon H. Ira, Jr., and Morton D. Bogdonoff, Durham, North Carolina

The development of electronic miniaturization has made possible radiotelemetry of physiologic data in man during situations in which previously available technics limited the individual's activities. In our laboratory, the initial clinical application of radiotelemetry has been made in continuous observations of the pulse rate before, during, and immediately after a night's sleep.

A small (4- by 10-cm.) FM transmitter sends an electrocardiographic signal from a precordial lead to a receiver located some distance from the individual's room. Continuous records of pulse rate have been made in 3 groups of patients: (1) "normal" individuals, (2) "anxious" individuals with increased CNS arousal, and (3) individuals with hyperthyroidism.

In group 1, the average sleeping rate ranged from 48 to 62 beats/min., and the average awake pulse was 57 to 90. In group 2, the sleeping pulse averaged 60 to 80, and awake pulse averaged 76 to 110. In group 3, the sleeping pulse averaged 108 to 118 with frequent rises up to 141; the awake pulses were in the same range. In addition, this technic provides indirect data on muscular activity during sleeping hours; it was observed that the hyperthyroid patients demonstrated a marked increase in activity.

These observations indicate that (1) radiotelemetry may be reasonably applied in clinical situations; (2) the increase in heart rate of individuals with CNS arousal persists to a minor degree during the sleeping state; and (3) the increased heart rate of hyperthyroidism persists strikingly during sleep, suggesting that increased cardiovascular activity in some patients may be independent of the CNS arousal accompanying the waking state.

New Technic to Measure Total Coronary Flow

David Irving and Eliot Corday, Los Angeles, California

The authors have utilized a new electronic technic for direct measurement of the total coronary blood flow. Using the new square-wave electromagnetic flowmeters simultaneously on the pulmonary artery and aorta, measurements were made of right and left ventricular outputs. Subtraction of the volumes of the aorta from pulmonary artery gave the amount of blood which had flowed through the coronary bed. The bronchial blood flow was ligated so that it could be disregarded.

This technic is more accurate because the heart is not touched and because it eliminates extraneous factors, such as coronary vasospasm, destruction of vasomotor apparatus, and artificial resistances.

Comparative Study of Prostheses for the Outflow Tract of the Right Ventricle

Takashi Iwa, Egbert H. Fell, Milton Weinberg, and Jay B. Hill, Chicago, Illinois

A prosthesis is required to enlarge the outflow tract of the right ventriele in hearts of patients with certain types of infundibular stenoses. The object of this report is to present our experiences in attempting to find a satisfactory prosthesis.

Under either hypothermia or cardiopulmonary bypass, 50 dogs were operated. A 4- by 2-cm. defect was created in the outflow tract of the right ventricle, including the anterior cusp of the pulmonary valve. In its place, a prosthesis of one of the following was sutured: (1) autogenous pericardium, (2) autogenous muscle, (3) autogenous diaphragm, (4) homogenous aorta, or (5) Teflon.

The dogs have been followed up to 7 months. The prostheses were studied as to their advantages and disadvantages grossly, by selective angiography, and microscopically. These studies showed that Teflon, although not ideal, was superior to the other experimental prostheses, with homogenous aorta second. The autogenous pericardium, diaphragm, and muscle healed very well but showed marked constriction and scar tissue formation.

An Approach to the Prevention of Initial Attacks of Rheumatic Fever: I. Use of Fluorescent-Antibody Technic in Identification of Group A Beta Hemolytic Streptococci (P)

James M. Jablon, John A. Mazzarella, and Milton S. Saslaw, Miami, Florida

Prevention of initial attacks of rheumatic fever depends upon early and complete treatment of group A β-hemolytic streptococcal infections. Therefore, rapid identification of the presence of this organism is essential.

In the present program more than 3,000 throat cultures of school children, absentees as well as those present in school, were studied by the fluorescent-antibody technic, alone or in combination with standard bacteriologic procedures. Throat swabs were incubated at 37 C. in broth for 3 hours. The bacterial sediment was used for streaking plates and preparing slides for fluorescein antibody staining.

The results indicated that the fluorescent-antibody technic is an excellent screening procedure. Throat cultures negative by fluorescence proved to be negative by the usual bacteriologic technic in 98 per cent of the cases studied by both methods (574 of 584 cultures). Swabs positive bacteriologically showed good correlation with fluorescence (65 of 76 cultures, or 85.5 per cent). However, the use of the fluorescent-antibody technic has limitations because of: (1) occasional cross reactions with other groups of streptococci, and (2) presence of streptococci on throat swabs which show good fluorescence but fail to grow culturally either because the organisms are not viable or normal bacteriologic methods are inadequate.

The principal use of the fluorescent-antibody technic is 2-fold: (1) prompt screening of negative throat swabs and (2) quick identification of group A streptococci in throat cultures.

The information obtained by this technic may thus be used as a guide for the early treatment of streptococcal infections.

Comparative Value of the Angiotensin Skin Test and the Cold Pressor Test

Benjamin Jablons, New York, New York, Loreto S. Santiago, Malabon-Rizal, Philippine Islands, Agapito DelRosario, and Paquita S. Mannulat, Manila, Philippine Islands

Angiotensin II amide, a synthetic valine-5 octapeptide, injected intradermally, produces a characteristic localized vasoconstriction, which persists for shorter periods in normotensives as compared with hypertensives. This angiotensin skin test (A.S.T.) has been found of additive value in the diagnosis of potential and established hypertension.

Studies were made of the value of the A.S.T., as compared with the cold pressor test (C.P.T.), in the differential diagnosis of normotensives and hypertensives. Thirty-one subjects, 35 to 86 years of age, 18 males and 13 females, 20 hypertensives and 11 normotensives, were tested by both methods. The hypertensive group was further subdivided into 10 untreated and 10 under treatment with antihypertensive drugs. All subjects were injected intradermally with 0.1 μg. of synthetic angiotensin and the time duration noted. Shortly thereafter, the cold pressor test was performed. In the normotensive group (11 cases), the A.S.T. persisted for 30 minutes or less in 8, and 60 minutes in 3. In the hypertensive group (20 cases), A.S.T. persisted 60 minutes or more in 19 and 30 minutes in 1. In the hypertensive group, C.P.T. was positive in 13 and negative in 7. In the normotensive group, C.P.T. was in agreement in 5 and at variance in 6. In the hypertensive group, the 10 treated showed that A.S.T. persisted for 60 minutes or plus in 9, and 30 minutes in 1, C.P.T. positive in 6 and negative in 4; in the 10 untreated, A.S.T. persisted 60 minutes plus in all 10, C.P.T. was positive in 7 and negative in 3. In our series the angiotensin skin test proved more consistent as a differential diagnostic test than the cold pressor test.

Physiologic Action of Epinephrine on the Fetal and Maternal Circulatory Systems

Benjamin T. Jackson, George J. Piasecki, and Richard H. Egdahl, Richmond, Virginia

The effects of epinephrine on the fetal circulatory system after both maternal and fetal injections of epinephrine were investigated. Experiments were carried out in the pregnant dog with the fetus entirely in utero throughout. New technics for in utero fetal operations and direct multilead fetal electrocardiography were utilized. In all experiments both fetal and maternal arterial pressure and electrocardiograms were obtained. Uterine artery blood flow was measured with an electromagnetic flowmeter. It was found that: (1) Epinephrine, 1 μg., injected intravenously into the fetus led to a significant rise (10 to 20 mm. systolic) in fetal arterial pressure with a slight increase in heart rate. (2) Epinephrine, 0.1 mg., injected intravenously into the mother resulted in a definite increase in maternal arterial pressure and heart rate and a transient increase in uterine artery flow, with subsequent marked and more prolonged decrease in flow, e.g., from 60 cc. per minute to 15 cc. per minute and to a decrease in fetal heart rate. (3) Simultaneous injection of 1 μg. of epinephrine intravenously into fetus and 0.1 mg. intravenously into mother was followed by a rise in fetal arterial pressure similar to that which occurred in fetal injection without maternal injection. Thus (1) the fetus responds to the direct injection of epinephrine with increase in blood pressure. (2) Epinephrine given to the pregnant female causes a sharp fall in uterine-artery blood flow, which, at least in part, may be responsible for the fetal hypotension that follows. (3) Epinephrine given directly to the fetus has at least a transient protective effect on the fetus in the circumstance of the decreased uterine blood flow that follows maternal epinephrine administration. (4) Epinephrine does not appear to cross the placenta in an active form under the conditions of this study.

Reassessment of the Blalock vs. Potts Operation: Observations on Animal Growth in the Presence of an Artificial Patent Ductus Arteriosus

Julius H. Jacobson II, Ernesto L. Suarez, Burton S. Tabakin, John S. Hanson, and Edgar J. Caldwell, Burlington, Vermont

Despite the advent of open heart surgery the systemic- to pulmonary-artery shunt remains a valuable procedure in selected cases. The Potts operation has had to be used in the infant age group because of the small vessel sizes. The Blalock operation (subclavian- to pulmonary-artery shunt) is preferable to the Potts operation (aortic- to pulmonary-artery shunt), primarily because of the ease with which it can be taken down at subsequent corrective surgery, and also because of difficulty in controlling exact size of the Potts-type anastomosis.

A method has been developed giving consistently good results in even the smallest vessels that are encountered surgically, thus allowing the Blalock operation to be used in all cases. The actual vascular anastomosis is carried out at 25 to 40 magnifications, utilizing a surgical dissecting microscope. Special instrumentation is described.

Ten pure-bred puppies, weighing from 4 to 7 pounds, had left subclavian- to pulmonary-artery shunts performed. Two animals died immediately after surgery. Seven dogs have survived to the present with fully open shunts, as demonstrated by retrograde aortography. One dog died 6 months postoperatively of distemper, and postmortem examination demonstrated patency of the shunt. A control group of 8 litter-mates underwent thoracotomy and division of the left subclavian artery. Growth rates in the 2 groups have been identical during the 10 months of postoperative observation. Thus (1) the subclavian- to pulmonary-artery shunt should be carried out in preference to the aortic- to pulmonary-artery shunt in even the smallest infants. (2) From experimental work

there is no indication that a left-to-right shunt the size of a patent ductus arteriosus interferes with growth.

Ventricular Systole as a Venous Pump

Frederick G. Joachim, Madison, Wisconsin

There is an unrecognized factor in venous return. Because of a brief functional rigidity of the mediastinum during ventricular systole, the contracting ventricles fill the atria reciprocally, as retraction of a plunger fills a syringe. The parietal pericardium is firmly attached to the sternum, ribs, and diaphragm; the heart is fixed at the base by the great vessels. The pleural surfaces are stabilized by the elastic recoil of the lung and the inertia of lesser-circulation blood. During the one-fifth second required for ventricular systole, regardless of the pulse rate, the cardiac mediastinum is functionally a rigid walled compartment. As the ventricles deliver their stroke volume into the aorta and pulmonary artery, an equal volume must reciprocally enter the atria from the cavae and pulmonary veins.

Serial x-rays of the heart during exercise or rest show changes in cardiac contour during various stages of the heart cycle but little change in volume, indicating that the atria fill as the ventricles empty.

Flowmeter studies show an acceleration of venous flow in the cavae with ventricular systole. Heart size and cardiac output decrease by 25 per cent when the chest is open. Distress with pneumothorax is out of proportion to decrease in tidal air. The concept of rigid mediastinum and reciprocal venous pump make these observations explicable. Analyses of jugular and atrial x′ waves must be revised to include this pump effect. Clinical applications are many.

Timed Vector Ballistocardiogram

Varner J. Johns, Jr., Ronald H. Selvester, and Ronald M. Moore, Los Angeles, California

Ballistocardiograms demonstrating the mechanical movements of the body in response to movements in the circulation have been recorded not only in the longitudinal axis of the body, but in 3 directions simultaneously, and the spatial vector of these movements has also been recorded as a vector ballistocardiogram. The disadvantages of the vector ballistocardiogram are the superimposition of the H, I, J, K, L, M, and N loops and the inability to evaluate time relationships between them. The simultaneous 3-dimensional ballistocardiogram clearly depicts the time relationships. However, the instantaneous spatial vector at various times during the cardiac cycle is often difficult to depict or visualize, and requires laborious arithmetical construction for each of these forces.

The timed vector ballistocardiogram combines the advantages of each of these methods by providing a simplified graphic method of photographing the spatial vector ballistocardiographic loops along a continuous, timed axis. The face of the oscilloscope of our vector ballistocardiogram was photographed with a V-70 Continuous Oscilloscope Recording Camera, the shutter remaining open and the film moving at a constant speed.

Twenty-five normals and 25 patients with organic heart disease were studied to evaluate the feasibility of this method. Conventional ballistocardiograms, vector ballistocardiograms, and timed vector ballistocardiograms were recorded in all. This produces a continuous tracing in which the H, I, J, K, L, M, and N waves are related to time in a manner similar to that in the conventional ballistocardiogram, while the spatial vector forces are clearly depicted in loops that are comparable to those seen in the vector ballistocardiogram but separated from each other so that each can be readily identified and its spatial magnitude and direction clearly shown.

Interobserver Variation in Blood-Pressure Recording by 48 Examiners in an Epidemiologic Study

Benjamin C. Johnson and Joseph de la Puente, Ann Arbor, Michigan

Quantitative estimates of interobserver variability are important in clinical practice and in epidemiologic studies. With regard to blood pressure, an analysis was made of 8,371 systolic recordings taken during an epidemiologic study in Tecumseh, Michigan. Single readings were obtained in a standard setting by 48 examiners, mostly junior attending staff physicians. Interobserver variability in systolic blood-pressure recording is reported; data on diastolic pressure are being analyzed. Random allocation of subjects to examiners is assumed. Estimates of variability were related to expected population values. Means of systolic pressure were calculated for each examiner within each of 30 age-sex groups. These were related to the population means for each group, as well as to the standard deviation and the number of persons examined by each physician. Thus, a standard normal deviate score was calculated to demonstrate across all age-sex groups whether an examiner showed undue variability, and whether his readings were predominantly above or below expected population values, as shown by a sign test. Four examiners read significantly high, while 6 examiners read significantly low ($p < 0.05$); 7 of these 10 were also suspect

on the basis of excess variability. Two others were suspect because of excess variability alone. In total, 12 examiners (25 per cent) were suspect on either excess variability or predominantly high or low readings, while 7 (15 per cent) were suspect on both counts. Detailed analysis of the several sources of variability is being undertaken. These variations do not invalidate inferences from blood-pressure distributions in population studies or groups of individuals involving multiple examiners, but must be taken into account in their evaluation and interpretation.

Changes in Technic That Improve Radioisotope Myocardial Blood-Flow Determinations

Philip C. Johnson, Houston, Texas

A method for estimating myocardial blood flow using a radioactive surface counting method was described about 2 years ago. Preliminary work showed significant decreases in myocardial flow in patients with atherosclerotic heart disease with or without myocardial infarction when these flows were compared to those in normals. In addition, nitrates were shown to produce statistically significant increases in myocardial flow.

This new method for estimating myocardial blood flow has been rightfully criticized because it evolves uncertainties in placement and in slope of the 2 extrapolations used to define the coronary flow area, because the formula used represents a new and still inadequately proved concept for measuring branched flow, and because it contains problems inherent to all surface counting technics. Whether this method estimates coronary flow quantitatively or whether it measures only relative changes in flow is still to be proved. Using this method in routine clinical practice, we have been able to institute changes in instrumentation that result in more reproducible curves and may remove some criticism of the method. These new curves have necessitated the development of an empirically derived technic for routine extrapolation which produce better and more reproducible clinical correlations as tested by double-blind technics. Continued animal and human studies have allowed us to define more accurately the necessary steps for obtaining reproducible curves and for obtaining a more precise estimation of myocardial flow.

These technical changes have produced additional evidence that this method estimates myocardial blood flow quantitatively.

Modification of the Hemodynamic Response to Exercise by Interference with the Autonomic Nervous System

Richard L. Kahler, Thomas E. Gaffney, and Eugene Braunwald, Bethesda, Maryland

In order to assess the contribution of the autonomic nervous system to the hemodynamic response to exercise, 6 normal subjects were studied at rest and during steady-state leg exercise in a control period without drugs and after pharmacologic interference with the autonomic nervous system. The latter was accomplished by the oral administration of guanethidine for 21 days, with the maximal daily dosage ranging from 60 to 65 mg., and atropine (2 mg. I.V.). During the control study, exercise requiring a 4- to 5-fold increase in oxygen consumption resulted in average increases above resting values in heart rate of 68 per cent, stroke volume 17 per cent, cardiac output 95 per cent, left ventricular minute work 147 per cent, and A-V O_2 difference of 141 per cent. However, with both guanethidine and atropine, identical exercise resulted in average increases above resting values in heart rate of only 28 per cent, stroke volume 4 per cent, cardiac output 30 per cent, left ventricular minute work 7 per cent, and A-V O_2 difference of 238 per cent. The absolute levels of stroke volume, cardiac output, and ventricular work were significantly lower, while A-V O_2 differences and heart rate were greater, when the exercise was carried out after guanethidine and atropine than during the control study. These data indicate that combined pharmacologic inhibition of the sympathetic and parasympathetic nervous systems interferes with the normal cardiovascular response to exercise.

Experimental and Clinical Experience with a New Implantable Cardiac Pacemaker (P)

Adrian Kantrowitz, Richard Cohen, Brooklyn, New York, Heinz Raillard, and Jack Schmidt, Syracuse, New York

A new, miniaturized, completely self-contained, implantable cardiac pacemaker has been developed. It measures 5 cm. in diameter, 1.5 cm. in thickness, and weighs 3 ounces. The circuit contains highly reliable components, including 2 transistors, 1 diode, and specially constructed batteries. The entire unit is encapsulated in a Teflon sheath. Two stainless steel electrodes maintain the contact with the myocardium. An optional transistorized external circuit has also been constructed which permits the patient to alter his pulse rate continuously from 64 to 120 beats per minute. There is no physical connection between the external control circuit and the implanted pacemaker. Without the external control circuit the pacemaker runs at a constant 64 beats per minute. The expected battery life is from 3 to 5 years. The unit was developed as a joint effort between the Department of Surgery of Maimonides Hospital of Brooklyn and the Advanced Circuits Division of

the General Electric Company. At this writing 2 patients have been operated upon, and 2 more are being prepared for surgery. Data on excitability of the human myocardium has been gathered which suggests that the threshold of excitability appears to be constant for the energy put in rather than for either the voltage or the amperage. The unit has been satisfactory. It is suggested that this is an effective method for the treatment of intractable Stokes-Adams syndrome.

Natural Course of Ventricular Septal Defect (P)

Samuel Kaplan, Georges I. Daoud, Irving H. Glass, Abraham Shemtob, and Johnson McGuire, Cincinnati, Ohio

In an attempt to evaluate the natural history of isolated ventricular septal defect (V.S.D.), 349 patients with this anomaly were studied. The clinical material consisted of the following: (1) proved by physiologic studies (cardiac catheterization, etc.), 105 patients; (2) confirmed at autopsy, 51 patients; (3) clinical diagnosis, 193 patients. It is appreciated that the latter group are not proved instances, but it is believed that the diagnosis can be established by clinical and routine laboratory methods.

The following conclusions were made: (1) From the autopsy material: (a) The period of highest mortality was in the first 2 years of life especially between the ages of 1 to 6 months (17 per cent). (b) The only deaths recorded between the ages of 2 to 16 years occurred after surgery for V.S.D. (c) Review of 6,983 consecutive autopsies in adults revealed 4 instances of V.S.D. (age 78, 29, 39, and 25 years). (2) Pulmonary hypertension was equally distributed in all age groups, but a change in pulmonary arteriolar resistance from slight or moderate to extreme elevation was not recognized. (3) In 22 adults, 59 per cent had slight to moderate left-to-right shunts, but in 41 per cent the pulmonary-artery pressure was at systemic levels. (4) Bacterial endocarditis occurred in less than 1 per cent of patients. (5) Spontaneous closure of large V.S.D.'s is rare but has been observed in 1 patient. (6) Hypertrophy of the crista supraventricularis occurred frequently, but the development of the clinical picture of tetralogy of Fallot was uncommon. (7) In the majority of patients, a small V.S.D. does not produce symptoms and deterioration of the pulmonary circulation is not common in this group.

Prolongation of the Phonocardiographic Q-1 Interval in Patients with Ventricular Septal Defects and Left-to-Right Shunts (P)

James N. Karnegis and Yang Wang, Minneapolis, Minnesota

Patients with large ventricular septal defects and left-to-right shunts may have a delayed closure of the mitral valve. This delay in closure may be detected from the phonocardiogram by measuring the Q-1 interval, that is, the interval from the onset of ventricular depolarization to the beginning of the rapid vibrations of the first heart sound.

Nine patients with uncomplicated ventricular septal defects and left-to-right shunts were studied by phonocardiography and right-heart catheterization. The Q-1 interval was measured from the tracing recorded at the apex with lead II of the electrocardiogram as time reference. The Q-1 interval in normal patients was taken to be 0.07 seconds or less.

In the 9 patients studied, there was no clinical or catheterization evidence of mitral valve disease. The Q-1 interval ranged from 0.06 to 0.10 seconds. The left-to-right shunt varied from 21 to 85 per cent. The prolongation of the Q-1 interval paralleled closely the size of the left-to-right shunt. It is suggested that the amount of flow through the mitral valve is a major determinant of the time of closure of the valve in patients with large ventricular septal defects and left-to-right shunts. One possible explanation is that the position of the mitral-valve cusps at end-diastole is influenced by the large flow. The resultant force of ventricular systole acting to effect closure of the mitral valve is thus diminished and the closure delayed.

Distinction between the Roles of Perfusion Failure and of Hypoxia in the Weakening of Ventricular Contraction during Local Ischemia

Frederic Kavaler, New York, New York, and Raul Mejia, Buenos Aires, Argentina

Electrical activity of the dog's heart, which becomes undetectable within minutes after interrupting coronary perfusion, has been reported to be present for an extended period under total perfusion with oxygen-poor blood during cardiopulmonary bypass. The present study attempts to show that contraction of ischemic myocardium, an apparently more oxygen-dependent property, is also compromised sooner by perfusional than by hypoxial factors. In the thoracotomized dog, the anterior descending branch of the left coronary artery was rapidly cannulated with short lengths of polyethylene tubing at 2 closely spaced sites 3 to 4 cm. from its origin. The ends of the tubing were inserted in a 3-way stopcock, so that normal continuity of flow could be maintained or interrupted, or the distal portion perfused with a fluid other than arterial blood. The local contractile record (from a shortening gauge) was profoundly altered in the ischemic area, the normal systolic shortening being replaced by a lengthening of the

muscle during systole within 45 seconds after interrupting the flow in the anterior descending branch, appreciable alteration in contraction appearing within 6 seconds. The abnormal contractile behavior was readily reversible on re-establishing flow. The anterior descending branch was perfused with venous blood (70 per cent saturated) for 6 minutes and with Tyrode's solution for 45 seconds. Contractions remained unchanged in both cases when ischemia resulted in an essentially flat contractile record after 20 seconds.

Surgical Treatment of Aortic Valvular Disease with Artificial Valves

Earle B. Kay, David Mendelsohn, Jr., and Henry A. Zimmerman, Cleveland, Ohio

During the developmental phase of aortic valvular surgery all of the various partial or palliative technics for surgical correction were employed. Though benefit was gained in many patients, we were never assured that maximal benefit had been provided in a sufficiently high incidence to justify the high operative mortality and morbidity.

Greater success in our minds could be afforded such patients by (1) the use of a competent artificial valve, (2) optimal myocardial protection during surgery, and (3) proper selection of patients prior to irreversible left ventricular failure.

The diagnostic tests for evaluation of patients, and the criteria for patient selectivity in 35 patients having surgical correction by means of artificial valves have been established. Twenty-seven patients had pure regurgitation and 8 calcific stenosis. There were 4 operative deaths. Myocardial metabolism studies were made which led to the employment of cold arrest followed by direct coronary artery perfusion of hypothermic blood for myocardial protection. Postoperative evaluation studies of valvular and myocardial function were also made.

Surgical Treatment of Mitral Insufficiency and Combined Mitral Stenosis and Insufficiency

Jerome H. Kay and Oscar Magidson, Los Angeles, California

Thirty-four patients have been operated upon for pure mitral insufficiency or mitral insufficiency with mitral stenosis using open technic with the heart-lung machine.

Five types of valves have been encountered. (1) Stenosis of the anterolateral commissure and insufficiency at the posteromedial commissure. (2) The type with stenosis of both commissures and insufficiency at the center of the valve. These have been treated by opening the areas of stenosis and closing the annulus at the posteromedial commissure. (3) In this type the only defect is dilatation of the annulus, treated by closing the annulus at the posteromedial commissure. (4) This type of valve consists of rupture of the chordae tendineae and dilatation of the annulus. In these patients the involved aortic or mural leaflet of the mitral valve is sutured to the papillary muscle at the site of the ruptured chordae tendineae and then the annulus at the posteromedial commissure is narrowed if necessary. (5) The fifth type is seen after closed mitral commissurotomy and consists of the previously made false cut in the mural or aortic leaflet. This is sutured and the stenosis is corrected.

The results with these patients have been excellent. There have been 5 deaths in the 34 patients operated upon: 3 occurred in the first 6 patients; 2 in the last 28 patients. Three deaths were in patients with right-sided heart failure with tremendous hearts. Many of these patients no longer have any murmurs.

Variations in "Pulmonary" and "Central" Blood Volumes in Normal Subjects

John F. Keighley, Harold Smulyan, Charles R. Markason, and Robert H. Eich, Syracuse, New York

Precordial monitoring technics were applied in studying the pulmonary blood volume (PBV) in 22 normal subjects.

Cardiac output (COP) and central blood volume (CBV) were determined by the indicator-dilution technic utilizing I^{131} labeled albumin or iodopyracet and interrupted brachial-artery sampling. Simultaneously, the passage of isotope through the right and left heart was monitored by 2 identical systems, each consisting of a 2-inch NaI scintillation probe, radiation analyzer, and scaler modified to record counts/unit time on an oscillograph. The mean transit time past each probe was determined from individual semilogarithmic plots. PBV was calculated as the product of probe-to-probe transit time and COP.

In 7 subjects, an antigravity suit was used to increase central venous pressure and decrease COP. The CBV tended to fall (dx: -0.166 ± 0.174 L./M.^{2}), whereas the PBV remained the same or rose ($d\bar{x}$: $+0.035 \pm 0.054$ L./M.^{2}). These changes were not significant when compared with a separate series of 7 subjects studied for reproducibilty.

After norepinephrine infusion at 7.6 μg./min. for 10 minutes in 3 subjects, a small change in COP (—12.8 to +3.5 per cent) was accompanied by a rise in CBV, while the PBV remained unchanged or increased slightly. In 3 subjects, when the COP fell more than 20 per cent, both CBV and PBV decreased.

Two subjects, infused with isoproterenol (1 μg./min. for 10 minutes), had a large rise in COP and CBV ($d\bar{x}$: +0.597 L./M.^{2}), but PBV remained essentially unchanged ($d\bar{x}$: +0.005 L./M.^{2}).

Variations in CBV may not reflect the magnitude or direction of PBV changes, the small range of which suggests that this volume is closely regulated in normal subjects.

Effect of Cigarette Smoking on Free Fatty Acids in Patients with Myocardial Infarction (P)

Alfred Kershbaum, Samuel Bellet, Raymond F. Caplan, and Leonard J. Feinberg, Philadelphia, Pennsylvania

In a study previously reported from this laboratory it was found that cigarette smoking caused a rapid and consistent rise in serum free fatty acids (FFA) in normal subjects and in patients with various clinical disorders. This effect probably resulted from a nicotine-induced catecholamine release that mobilized FFA from adipose tissue stores. In the present study, similar experiments were performed in 17 patients with healed myocardial infarction. Two cigarettes were smoked in a 10-minute period and the serum FFA concentration was determined before and after smoking and 10, 20, and 40 minutes later. The FFA levels rose at the end of the smoking period in all subjects, and the maximal elevation usually occurred 10 to 20 minutes later. The maximal rise of FFA above the presmoking level ranged from 345 to 2304 μEq./L. with a mean rise of 858 μEq./L. (65.6 per cent). In previously studied subjects with no myocardial infarction the maximal FFA elevation after smoking ranged from 98 to 840 μEq./L., with a mean of 351 μEq./L. (30.0 per cent). The more marked rise in FFA levels after smoking in the subjects with myocardial infarction can be explained by a greater release of epinephrine and norepinephrine by the absorbed nicotine or by a reduced utilization of the mobilized FFA in these individuals.

Effect of Cigarette Smoking on the Fibrinolytic Activity of Plasma in the Human Subject

Alfred Kershbaum, Samuel Bellet, Raymond F. Caplan, and Herschel Sandberg, Philadelphia, Pennsylvania

Recent observations have established that increased thrombolytic activity occurs after certain stressful situations and after the administration of epinephrine. Cigarette smoking gives rise to an increase in circulating epinephrine and norepinephrine as a result of the sympathetic- and adrenal-stimulating effects of the absorbed nicotine. In a previous study reported from this laboratory, it was shown that shorter lysis times occurred in various fibrinolytic parameters after the infusion of nicotine and related compounds in dogs. In the present investigation, the effect of smoking on fibrinolytic activity was studied in 11 human subjects. Two cigarettes were smoked within a 10-minute period and blood was drawn before and 10, 20, and 40 minutes after smoking. Fibrinolytic activity was determined by the following studies: (1) the lysis time of a standard fibrin clot by undiluted plasma; (2) the lysis time of a standard fibrin clot by plasma diluted 1:10 and 1:20 in imidazole-saline buffer; (3) the lysis time of a standard fibrin clot by plasma to which had been added serial dilutions of streptokinase-activated human fibrinolysin. The lysis times were shortened after smoking in every instance in each of these 3 parameters. The average lysis times were shortened respectively to 81.5 per cent, 86.0 per cent, and 84.8 per cent of the presmoking control lysis times. These findings indicate that a significant increase in fibrinolytic activity occurs in human plasma after cigarette smoking.

Response of Free Fatty Acids (FFA) to Ethanol Administration: Studies in Dogs and Man

Alfred Kershbaum, Samuel Bellet, Lily Ruckstuhl, and Hadi Dizadji, Philadelphia, Pennsylvania

Several recent studies have shown that ethanol administration causes an increased secretion of epinephrine and norepinephrine, and the question arose whether this increase in circulating catecholamines results in a mobilization of FFA. In fasting, anesthetized dogs, 14 experiments were performed in which intravenous ethanol was given in a dose of 0.60 Gm./Kg. as a 16 per cent solution within a 10-minute period. Blood samples were taken from a femoral vein at intervals of 10 to 30 minutes for a period of 120 minutes. The mean maximal elevation of serum FFA after ethanol (591 μEq./L.) was less than the mean maximal elevation (643 μEq./L.) in controls (fasting animals not receiving ethanol). In 4 experiments in unanesthetized animals, the mean rise of FFA after ethanol (72 μEq./L.) was markedly less than in control experiments (2074 μEq./L.); the more marked rise in these control dogs was probably due to a greater catecholamine release incident to excitement when no anesthesia was used. In 15 fasting human subjects, studies were made in which 2 ounces of 94.6 proof whiskey were taken orally and venous FFA levels were obtained before and at intervals after imbibition for 60 minutes. Control levels were similarly obtained in the same subjects, without whiskey being given. After whiskey

all subjects showed lower FFA levels within 10 to 40 minutes (mean reduction of 334 μEq./L.). All controls had a rise of FFA (mean of 133 μEq./L.). The reduction in FFA levels in man and the suppressed elevation in dogs in the peripheral venous circulation after ethanol may indicate that this drug can cause a decrease in FFA release from fat depots or an increase in FFA consumption in the peripheral tissues.

Correction of Mitral Insufficiency Using Extracorporeal Circulation and Mild Hypothermia

William J. Kerth and Frank Gerbode, San Francisco, California

Operations on the mitral valve have in general been less satisfactory than other open-heart procedures. In an attempt to develop a better procedure for mitral insufficiency, hearts of patients who died from mitral insufficiency and a series of normal hearts were studied using a simple pulse duplicator.

The sine qua non of good mitral-valve function is a mobile aortic leaflet which approximates the posterior or mural leaflet. By opening the frequently fused anterior commissure, freeing fused chordae tendinae, and occasionally removing calcium from the aortic leaflet, it can be made mobile and functional.

In both series of hearts studied with the pulse duplicator and in operative cases of mitral insufficiency, we have found that clefts in the posterior leaflet of the mitral valve could be sutured, thereby making it oppose more perfectly to the aortic leaflet. We have also found it possible to remove calcium from the posterior leaflet and frequently gain substance as well as mobility.

Using a combination of these procedures we have found it possible to correct mitral insufficiency in a series of consecutive patients. We have not found it necessary to use annuloplasty in any of these. The operative appearance of the valve and the short-term follow-up on these patients have been very gratifying.

Reflex Oscillation of Flow and Resistance in Mayer Waves (P)

Thomas Killip, III, Stockholm, Sweden

Particiapation of baroceptor and chemoceptor reflexes in the regulation of blood pressure is well recognized, but knowledge of their role in the distribution of blood flow is incomplete. In animals and humans, rhythmic oscillations in blood pressure, termed Mayer waves, may occur under certain conditions. Since they are apparently due to an alternating feed-back between chemoceptor and baroceptor discharge, measurement of associated alterations in flow would provide further understanding of the reflex control of the circulation.

Mayer waves were produced in chloralose-anesthetized cats by graded hemorrhage. Organ blood flow was measured with photoelectric drop counters, while perfusion pressure was maintained constant by a special device.

Rhythmic oscillation in arterial pressure as great as 80 mm. Hg was observed. Changes in right ventricular pressure lagged behind those in the left ventricle. Flow cycles in the abdominal aorta and vena cava were also out of phase; the surge of venous return followed by 4 to 6 seconds the aortic flow and pressure rise. Vascular resistance in the kidney did not fluctuate. In both muscle and intestine, however, Mayer waves were accompanied by rhythmic increase and decrease in vascular resistance with as much as a 3-fold change. Skin resistance changed slightly.

These results suggest that reflex mechanisms producing Mayer waves affect vascular resistance primarily in the muscular and mesenteric beds. Despite extensive sympathetic innervation, changes of flow in skin and kidney are essentially passive.

Incidence of Beta Hemolytic Streptococcus

Charles K. Kincaid, Evelyn C. Nelson, and Thayer W. Burnham, Madison, Wisconsin

Four hundred children in three Madison, Wisconsin schools, grade 4, had throat swabs twice a month, from December to June for 3 years. The highest number of swabs positive for β-hemolytic streptococcus at any one time was 124 among 411 children (30.2 per cent). Absentees received a home visit to collect throat swabs and an illness history. All positive cultures were grouped. The preponderance was group A. When the incidence of infection increased, it was due to an increase in this one group. A positive culture was more frequently associated with suggestive symptoms than with none; and, among those with symptoms, the group A was by far the most common. When symptoms were more severe, group A was present 50 times to a single such occurrence with a different group. Study of cultures on children who had received penicillin therapy showed that all but a few were "cleaned up." In dividing the study group according to presence or absence of tonsils, a difference evidently did exist, the presence of tonsils seeming nearly to double the frequency of finding a positive culture.

It became obvious that the group A streptococcus can exist in the throats of a few children almost continuously without obvious symptoms, perhaps living as a nonvirulent saprophyte. Whether or not such organisms ever regain their virulence for other children was not investigated.

Clinical Course of Chronic "Asymptomatic" Proteinuria

S. Edward King, New York, New York

Despite absence of history and of other clinical evidence of renal or vascular disease, astute clinicians long have been wary concerning prognosis in patients with chronic "asymptomatic" proteinuria of undetermined origin. Miscellaneous pathologic renal lesions, including glomerulonephritis, occasionally have been reported on renal biopsy in such patients.

Fifty young male patients with chronic "asymptomatic" proteinuria without history referable to the urinary tract and with normal urine sediment and blood pressure were followed over a mean interval of 6 years. They were studied initially during short periods of hospitalization, including examination of multiple freshly voided urine specimens. By accepted standards, this group conformed to the definition of chronic "asymptomatic" proteinuria. Patients were re-examined at varying intervals of between 5 and 7 years on several occasions. Clinical study included renal function tests, excretory urography by the method of Brod to detect early disparities of excretion, and urine cultures and cystoscopy as indicated.

Proteinuria increased in 28 of the 50. Appreciable sediment abnormalities: hematuria and/or pyuria with casts were demonstrated in 43. Hypertension (140/90 or above) developed in 24 patients. The clinical diagnosis of chronic glomerulonephritis was made in 10. Pyuria with casts, disparate excretory urograms, clubbing or obstructive uropathy, atrophic kidney, bacteriuria, hyposthenuria, and hypertension compositely justified the diagnosis of chronic, usually " inapparent," pyelonephritis in 31 patients. Azotemia developed in 11 of the 50 patients, 5 dying of renal insufficiency.

Prognosis in chronic "asymptomatic" proteinuria must be guarded. Diseases producing this clinical picture include chronic "inapparent" pyelonephritis, obstructive uropathy with infection, and chronic glomerulonephritis.

Latent (Cryptogenic) Chronic Glomerulonephritis

S. Edward King, New York, New York

The development of persisting orthostatic-type proteinuria with normal sediment after acute diffuse glomerulonephritis is well-known. This lesion has been designated as "healed with defect" by Addis. The occurrence of hypertension as the sole residue of acute diffuse glomerulonephritis also is recognized.

A documented history of prior, acute diffuse glomerulonephritis, often in childhood, was obtained in 14 of nearly 300 young males (mean present age 27 years) presenting clearly defined orthostatic type proteinuria when examined for military service, which persisted for 6 years or longer. Since even advanced chronic glomerulonephritis was frequently unrecognized prior to routine examination in such individuals, this occurrence probably is not infrequent. Studies were detailed, initially during hospitalization, and in each instance with multiple fresh urine examinations.

In 8 of these 14 patients, proteinuria absent during recumbency and mild during orthostasis or lordosis became intense (over 1 per cent) on mild exercise, usually with casts and microhematuria. Four of these 8 displayed resting blood-pressure levels of 140/90 or above.

The 6 remaining patients presented similar elevations of blood pressure with variable and, at times, constant proteinuria with casts and microhematuria. Depending upon findings on the individual occasion examined, the diagnosis of either "benign" orthostatic proteinuria or chronic latent glomerulonephritis could be justified.

Orthostatic proteinuria after acute diffuse glomerulonephritis may persist as an apparently fixed residual defect or as a latent, deceptively cryptogenic, but active variant of chronic diffuse glomerulonephritis.

Incidence of Hyperuricemia in 400 Hypertensive Patients

Dera Kinsey, Raymond Walther, Herbert S. Sise, George Whitelaw, and Reginald Smithwick, Boston, Massachusetts

Four hundred patients with hypertensive disease who were first studied and grouped according to the Smithwick criteria in the years 1944 to 1957 were restudied in 1960 to evaluate the different forms of therapy used in their treatment. Approximately one-third had been treated by lumbodorsal splanchnicectomy, while two-thirds received antihypertensive drugs or no treatment. Because of the authors' awareness that the uric acid level of the blood seemed frequently to be elevated in hypertensive patients, a routine determination was done on all patients seen in 1960 to determine the incidence and relationship to certain key factors. The level of uric acid was considered abnormal if over 6 mg. per cent in men and over 5 mg. per cent in women. More than 40 per cent (183 out of 400) of all of the cases had a high uric acid blood level. Thiazide derivatives were being taken by about one-half of the patients in both groups. The incidence of hyperuricemia was higher in patients receiving thiazide compounds in both surgical and nonsurgical groups, but was present in

one-third of those not receiving thiazides. Hyperuricemia occurred more frequently in men (52 per cent, 88 of 169) than in women (43 per cent, 95 of 221) and in surgically treated patients (59 per cent, 66 of 112) than in medically treated patients (42 per cent, 117 of 248). These differences, however, are not significant but are repeatedly seen in breakdowns into various groups, suggesting that they may be real. There was no correlation between kidney function and hyperuricemia unless the blood urea nitrogen was over 30 mg. per cent. There was no correlation with serum potassium or age of the patient. Clinical gout occurred in 14 patients (3.5 per cent) and was evenly distributed between the surgical and nonsurgical patients. There was a significantly higher incidence of hyperuricemia in those with severe hypertension (groups 3 and 4) compared to the more benign hypertension (groups 1 and 2). It is concluded that hyperuricemia is present in over one-third of the cases of hypertension and that, while thiazide administration and renal failure may increase the degree of hyperuricemia, the elevated blood levels are primarily related to the disease process itself.

Interpolated Ventricular Premature Systoles, Reciprocal Rhythm, and Multiple Pathways of Conduction

Albert D. Kistin, Beckley, West Virginia

This study indicates that the ventricular systole which follows an interpolated ventricular premature systole (VPS) is commonly due to reciprocal rhythm; the impulse of the interpolated VPS commonly travels retrograde to or toward the atria and somewhere in its course turns back to activate the ventricles again. Twenty-four unselected patients, each with both interpolated VPS and VPS followed by the more usual pause, were studied with simultaneous esophageal and standard electrocardiographic leads. Retrograde conduction to the atria was observed in 12 patients after the interpolated VPS and in 17 after the VPS followed by a pause. In 6 patients conduction times occurred in 2 distinct orders of magnitude suggesting 2 pathways of conduction. Multiple pathways of conduction are a possible mechanism for reciprocal rhythm.

Electrical Alternans in Single Fibers of Pacemaker and Specialized Conductive Tissue

Morris Kleinfeld, John Magin, and Edward Stein, New York, New York

The production of electrical alternans in single ventricular fibers of the frog by means of *l*-thyroxine or triiodothyronine and simultaneously induced acute hypoxia was reported previously. Electrical alternans has also been produced in single atrial fibers by means of *l*-epinephrine. This study was designed to demonstrate its occurrence in pacemaker and specialized conductive fibers.

Isolated perfused rabbit hearts and false tendons of beef hearts were used. The membrane action potentials were recorded by means of intracellular electrodes. Electrical alternans was produced in single fibers of the S-A node, the A-V node, and the bundle of His of the rabbit heart, and in single fibers of the false tendon of the beef heart by means of epinephrine and hypoxia. The phenomenon was transitory and unrelated to heart rate.

Three types of alternation were observed: (a) in the rate of depolarization; (b) in the rate of repolarization; and (c) in the magnitude of the membrane action potential. The alternation usually involved several phases of the action potential. Electrical alternans has now been produced in this laboratory in contractile, pacemaker, and specialized conductive fibers. The exact mechanism underlying its occurrence is still obscure, although almost certainly alternation in the rate or extent of electrolytic transfers across the membrane are involved.

Lysis of Experimental Coronary Thrombi

John L. Kline and Nils M. Ohlsson, Philadelphia, Pennsylvania

It has been our purpose to evaluate objectively the effect of fibrinolytic therapy on coronary thrombi produced in the experimental animal.

A reliable method of producing coronary thrombosis in the dog has been evolved. This was accomplished by the injection of topical thrombin through a no. 30 needle into an occluded segment of either the left anterior descending or the circumflex coronary artery. The presence of a thrombus was confirmed in every instance by coronary angiography and subsequent histologic sections or vinyl acetate casts of the coronary tree.

Of 50 animals, 18 went into ventricular fibrillation before fibrinolytic therapy could be instituted. The remaining 32 were subdivided into 3 groups for purposes of evaluating sinus of Valsalva injection of fibrinolysin. Group 1: 10 dogs were given 10,000 units per Kg. for the first 2 hours. Lysis was achieved in 3 instances. Group 2: 10 dogs received 30,000 units per Kg. for the first 2 hours with subsequent lysis in 5 cases. Group 3: 12 dogs received 30,000 units per Kg. over the first 24 hours with successful lysis in 8 instances. Lysis was confirmed in every one of the 16 successful cases by serial coronary angiography. There were 14 survivors in this group. Of 16 animals in which clot lysis was not achieved, 5 survived.

These results would indicate that lysis of a coronary thrombosis is possible if instituted immediately with high concentration of fibrinolytic agents injected into the sinus of Valsalva.

Breath-Holding Time as a Test for Chronic Hyperventilation

Robert M. Kohn, Buffalo, New York

Breath-holding time can be used as a screening test for functional cardiovascular disease. In 100 consecutive cases examined for cardiac evaluation, on the basis of history, physical, laboratory, and psychologic interview, 13 per cent were found to have primarily functional symptoms, even though some had true organic disease. All but 1 of these functional cases was unable to hold his breath for at least 20 seconds. With 1 exception, all the remaining 87 subjects, consisting of normals, those with pulmonary emphysema, and those with functional Class I, II, and III cardiovascular disease, could hold the breath for at least 20 seconds. No Class IV cases were tested. The sensitivity of this test could be increased by a 30-second period of hyperventilation before timing the breath-holding. Those people with short breath-holding times, presumably the chronic hyperventilators, were found to have low alveolar pCO_2's prior to the breath-holding attempt, rising only slightly at the breaking point. This agrees with the reported observation that the first day at high altitude produces no significant change in breath-holding time, but after acclimatization, with chronic hyperventilation, breath-holding time is significantly shortened. False-positive tests can be obtained from patients with organic disease characterized by hyperventilation without CO_2 retention, such as pulmonary fibrosis, multiple pulmonary emboli, and some cases of mitral stenosis. With these exceptions in mind, the breath-holding time is useful as a screening test for chronic hyperventilation.

In relaxed individuals acute hyperventilation lengthens or does not change breath-holding, chronic hyperventilation shortens it.

Artificial Heart in the Chest as a Permanent Substitute

Willem J. Kolff, Tetsuzo Akutsu, Wolfgang Seidel, and Velimir Mirkovitch, Cleveland, Ohio

Our aim was to construct a pump to replace permanently the irreparable human heart. Mechanical hearts, driven by solenoids or electromotors, have been described. Air-driven artificial hearts are lighter, smaller, and stronger, but require 1/8 inch I.D. tubing through the chest wall instead of electric wires. One air-driven heart consists of 2 plastic ventricles fitted into 2 slightly larger rigid housings. A second type uses 2 systems of pistons, each sealed by rolling diaphragms (Belloframs). In both models, venous pressure (V.P.) on either side regulates the output, e.g., for dog size heart V.P. 0 output, 500 ml.; V.P. 15 output, 2,800 ml. Tiny electrical wires lead from transducers on the ventricles and allow monitoring of stroke volume on the outside. Right and left heart are separated to facilitate insertion. Fifteen such hearts have been inserted in dogs after removal of their own hearts. The chest was then closed. Four dogs woke up, 1 drank, barked, and moved, but could not walk. It responded to petting in a manner suggesting absence of brain damage. Simultaneous pressure recordings obtained: left atrium, 4 mm. Hg; aorta, 140/90; right atrium, 5; pulmonary artery, 30/10. Mean pressures were normal, contours not. After heparin neutralization, clotting times (5 min.) and thrombocytes (150,000 to 200,000) were normal. No hemorrhages and no pulmonary edema occurred. Hemolysis, high (226 mg. per cent) after extracorporeal circulation, decreased to 150 in 9 hours. Survivals to 14 and 20 hours were obtained. The portal hypertension syndrome observed may have been due to insufficient pH correction.

Studies on Negative Blood Flow (Backflow) in the Dog Aorta

Peter A. Kot and John C. Rose, Washington, D. C.

A backflow phase in the pulsatile flow pattern has been noted in various segments of the aorta of animals and man. McDonald discussed this in relation to changes in the arterial beds both proximal and distal to the site of flow measurement. This phenomenon was studied in open-chest, anesthetized dogs, using an ultrasonic flowmeter (60 c.p.s.) in the descending thoracic aorta. Backflow is not prominent in this area in the steady state. When either pressor agents or vasodilator substances were injected intravenously, augmented backflow developed in early diastole during the period of readjustment of overall peripheral resistance. This effect was unaltered by ganglion blockade. These observations suggested a temporary differential in resistance of the upper and lower portions of the arterial circulation. To test this idea, vasoactive substances were selectively injected into major arteries above and below the point of flow measurement. In this manner, alterations of reverse flow were studied before the generalized systemic effects of the drugs occurred. When injected distal to the flowmeter (abdominal aorta), vasopressors caused marked backflow, while vaso-

dilators raised the level of the lowest portion of the pulsatile flow curve. When injected into the brachiocephalic artery, vasopressors prevented the development of a significant negative component, whereas vasodilators caused the appearance of backflow or augmented that which was already present. These observations suggest a protective mechanism. During acute generalized alterations in vascular resistance caused by drugs, backflow from arterial beds below the diaphragm ensures the maintenance of adequate cerebral and myocardial blood flow.

Effect of Extracorporeal Circulation upon the Tissue Digoxin Concentration in the Dog (P)

Nicholas T. Kouchoukos, David Goldring, and Robert M. Burton, St. Louis, Missouri

The effect of total-body perfusion with extracorporeal support upon the concentration of digitalis glycosides in tissues is not known. Therefore, the regulation of dosage in patients in the immediate postoperative period is very difficult.

Experiments were devised using 4 dogs which were digitalized with tritium-labeled digoxin (1 mg. digoxin was labeled with 50.9 μc. of tritium), 75-180 minutes prior to cardiopulmonary bypass using a Kay-Anderson heart-lung pump. During the 30 minute perfusion, blood samples were obtained every 5 minutes from the venous line of the pump (mixed venous blood of the dog). Arterial blood samples were obtained at 10-minute intervals (pooled blood of the heart-lung apparatus).

The animals were sacrificed and samples of heart, kidney, and liver were obtained. The samples of blood and tissue were analyzed for radioactivity using a Packard Tri-Carb liquid scintillation spectrometer with 2-channel pulse height analyzer.

Pieces of atrial muscle were obtained before and after bypass to evaluate the pattern of contractility for digitalis effect.

No radioactivity could be detected in the perfusion fluid of the heart-lung apparatus during bypass and none could be detected in the blood reservoir after perfusion.

The average concentration (3 dogs) of tritium-labeled digoxin in the heart muscle was 13.4 mμc./Gm. of tissue, in the kidney it was 57.4 mμc./Gm. of tissue, and in the liver it was 5.96 mμc./Gm. of tissue. These figures represented respectively 1.86 per cent, 8.2 per cent, and 3.65 per cent of the total administered tritium-labeled digoxin. These values were in the same range as in the control animal which was digitalized and did not undergo total-body perfusion.

The pattern of atrial-muscle contractility did not show a diminished degree of digitalization after perfusion.

This pilot experiment suggests that total-body perfusion does not appreciably affect the digoxin content of the heart, liver, and kidneys in the dog. Experiments are in progress to determine if this conclusion applies to man.

Open-Heart Surgery for Mitral Stenosis

John J. Kralik and Oscar Oca, Cleveland, Ohio

Where facilities are available, open-heart surgery may well be recommended as a routine procedure for patients with surgically significant mitral stenosis. Our experience with direct vision repair has been unusually gratifying. Nineteen consecutive patients have had open-heart surgery for rheumatic mitral stenosis and been followed from 1 to 22 months. There has been no early or late mortality.

The method appears to have the advantages of accuracy and completeness in dividing the commissures, avoidance of surgical mitral insufficiency, ease of handling clots that are either free in the atrium or lodged in the atrial appendage, and affording the surgeon the opportunity to correct mitral insufficiency should this be necessary. Recovery following surgery has been prompt. No serious complications have occurred. If the aortic valve is even slightly incompetent during the perfusion, there will be considerable mitral regurgitation as the valve is manipulated for the commissurotomy. In these instances direct vision commissurotomy is facilitated by opening the valve with a 2-bladed expandable dilator. Our perfusion time has varied between 25 and 62 minutes. The DeWall-Lillehei bubble oxygenator has been used for all 19 cases.

Contrasting Circulatory Adaptation in Two Hypermetabolic States

Frank W. Kroetz, William J. deGroot, James J. Leonard, Galveston, Texas, and James V. Warren, Columbus, Ohio

It is known, but not generally appreciated, that salicylate ingestion results in increased oxygen consumption that may reach the levels seen in severe hyperthyroidism. To compare the relative circulatory loads imposed by these 2 hypermetabolic states, hemodynamic studies were performed on 7 normal subjects before and after ingestion of 7.2 to 10.2 Gm. acetylsalicylic acid, daily, for 2 to 4 days (average serum salicylate level, 63 mg. per cent). The circulatory response was compared with that of 8 patients with clinical hyperthyroidism.

Salicylate ingestion resulted in a 45 per cent increase in oxygen consumption (139 to 202 cc./min./M^2., $p < 0.01$) but only an 18 per cent

increase in cardiac index (2.92 to 3.45 L./min./M^2., $p < 0.02$). Calculated arteriovenous oxygen difference widened from 4.8 to 6 vol. per cent ($p < 0.01$). In 8 hyperthyroid patients, at a similar level of oxygen consumption (188 cc./min./M^2., $p > 0.50$), there was a strikingly higher cardiac index (5.95 L./min./M^2., $p < 0.01$) and a narrowed calculated arteriovenous oxygen difference (3.5 vol. per cent, $p < 0.01$).

These studies demonstrate a marked difference in the circulatory adjustment to salicylate-induced hypermetabolism compared to hyperthyroidism. In salicylate-induced hypermetabolism there is a slightly increased circulatory load and a widened arteriovenous oxygen difference, while in hyperthyroidism there is a markedly elevated circulatory load and a narrowed arteriovenous oxygen difference.

These data support the concept that the hemodynamic response to thyroxine is determined by factors other than increased tissue oxygen requirements, and further demonstrate a more efficient circulatory response to increased metabolic demands in salicylate-induced hypermetabolism.

Recurrent Pleuropericarditis (Postcardiotomy Syndrome) after Open-Heart Repair of Congenital Cardiac Defects

Irving G. Kroop, Irving Carno, and Carl Oshrain, Brooklyn, New York

The postcardiotomy syndrome is defined as fever and pleuropericarditis occurring after the immediate postoperative febrile period, and preferably after an afebrile and asymptomatic interval of 1 week. All postoperative fevers without pleuropericarditis are excluded. The fever and recurrent pleuropericarditis which follow open-heart surgery are similar to the pleuropericarditis following mitral commissurotomy, myocardial infarction, and trauma to the heart and pericardium. All these instances of febrile pleuropericarditis are strikingly similar to idiopathic or viral pericarditis, including the tendency to recur with decreasing severity. Mechanisms to explain the syndrome have included: (1) trauma to the pericardium, (2) blood in the pericardial sac, and (3) an allergic autosensitization to the myocardial and/or pericardial tissues.

The data of 3 patients with pleuropericarditis after correction of an atrioseptal defect with cardiopulmonary bypass illustrate the clinical features of the syndrome and emphasize the dangers of steroid therapy and cardiac tamponade.

Since 1957, only 3 instances of the postcardiotomy syndrome have been encountered in a series of 57 patients requiring open-heart repair of a congenital defect. Two cases occurred in June, 1957, and 1 in October, 1960. These 3 cases followed atriotomy and there was no excessive bleeding into the pericardial sac. The 1 case of hemorrhagic cardiac tamponade after pulmonic valvulotomy was not followed by the postcardiotomy syndrome. Thus, the incidence of cases is low and the distribution not uniform. There was a high incidence of viral pericarditis at the time of operation in the last case.

Effects of Hypothermia and Extracorporeal Circulation in Myocardial Infarction with Shock (P)

Leslie A. Kuhn, Frank Weiser, Ronald Apter, and John E. D'Aria, New York, New York

Prolonged hypothermia was induced in 43 dogs after plastic-sphere coronary embolization. In 20 blood-stream cooled animals ventricular fibrillation (VF) occurred at an average esophageal temperature of 20.8 C. and arrest at 12 C. In 8 maintained by extracorporeal circulation at 5 to 10 C. for 5 hours, prolonged VF occurred but, on rewarming, defibrillation was successful in all. Of 14 kept at 28 to 30 C. for 4 to 5 hours, there was no arrhythmia. One of 11 skin-cooled dogs maintained at 28 to 30 C. fibrillated.

Cardiac output (CO), mean central aortic pressure (MAP), and left ventricular contractile force (LVCF) diminished after embolization, and systemic vascular resistance (SVR) increased slightly. In the blood-stream-cooled animals, CO, MAP, and LV work diminished progressively with increasing hypothermia. SVR and LVCF increased. LV diastolic and RA pressures were unchanged. Skin-cooled dogs maintained at 28 to 30 C. did not manifest a similar fall in CO, LV work, or a rise in SVR. Hypothermic animals demonstrated return to or near pre-embolic CO, MAP, SVR, and LVCF after rewarming. In contrast, 6 dogs remaining normothermic for 4 to 6 hours after embolization demonstrated no rise in CO or MAP.

It is concluded that a dog with acute coronary embolization and shock is not more sensitive to hypothermic arrhythmia than a normal animal and that there is little irreversible deleterious hemodynamic effect after 5 hours of profound or moderate hypothermia combined with extracorporeal circulation. Animals rendered hypothermic after embolization and then rewarmed demonstrate more adequate recovery of MAP, CO, and SVR than do those remaining normothermic for similar periods.

Partial Substitution of Cardiac Function over Prolonged Periods with a Mechanical Pump

Bert K. Kusserow and James F. Clapp, III, Burlington, Vermont

A small, portable, mechanical blood pump has been built that is intended for long-term partial substitution of cardiac function. Pumping action is attained by the gentle to-and-fro oscillation of a diaphragm that is driven by a mechanical cam-gear and electric motor complex. The pump may be placed either intracorporeally or paracorporeally in juxtaposition to the outer surface of the chest wall. It has been used to substitute partially for both ventricles at once, and also as a partial substitute for each ventricle alone. When used as a left ventricular assist, blood reached the pump from the cannulated left atrium and was returned into the aorta via the cannulated left subclavian artery.

A continuous perfusion of 53 hours has been accomplished in a conscious, ambulatory, anticoagulant dog with the pump in use as a left ventricular assist. In this experiment the pump was placed paracorporeally. Pump blood flow approximated one-fifth to one-third of total cardiac output. Arterial pressure tracings during such left atrial to systemic-artery perfusions suggest decreased cardiac work. Further studies pertaining to this point are in progress. Free plasma hemoglobin resulting from pump-induced erythrocyte destruction attained a value of 29.4 mg. per cent at the end of the longest perfusion to date (53 hours). Postperfusion white cell counts were generally increased over preperfusion controls. A yet unsolved problem is pump-induced thrombus formation and embolization.

Familial Cardiomegaly

W. J. Kuzman, A. M. Bassett, and K. M. Taylor, San Diego, California

Familial cardiomegaly is a distinct clinical, electrocardiographic, and pathologic syndrome originally described by William Evans in 1949. Isolated case reports have been recorded periodically. A review of the world literature disclosed a total of 43 previously documented cases. Recently we studied a family with familial cardiomegaly and carried out detailed clinical, physiologic, and genetic analyses in 14 family members extending over 3 generations. No sex difference was noted. Symptoms consisted of exertional dyspnea, fatigue, palpitations, and repeated embolic episodes. Variable systolic and diastolic murmurs were recorded. Electrocardiographic study disclosed rhythm disturbances in conjunction with left ventricular hypertrophy, bizarre QRS complexes, and varying A-V block. X-rays demonstrated gross cardiomegaly with selective left atrial and left ventricular enlargement, dilated main pulmonary artery, and pulmonary parenchymal changes consistent with pulmonary infarction. Physiologic study disclosed normal peripheral artery saturation and pressure, associated with a markedly reduced cardiac output. Elevated pulmonary-wedge and pulmonary-artery pressures were recorded and pulmonary resistance was elevated. Pathologic changes are those of gross enlargement with fibrotic and hypertrophic changes microscopically. Differential diagnosis includes all of the cardiomyopathies. Treatment was empirical and consisted of controlling failure and providing prophylactic anticoagulants. Genetic studies indicate familial cardiomegaly to be an autosomal dominant with varying degrees of penetrance.

Atrial Parasystole with Interpolation: Its Bearing on the Concept of Sino-atrial Block

Richard Langendorf, Chicago, Illinois, Milton E. Lesser, Paul Plotkin, and Burton D. Levin, Miami Beach, Florida

So far as could be ascertained the case presented here is the first reported observation of an atrial parasystole with interpolation of some of the ectopic atrial beats. This interpretation is based on the analysis of the considerable variations of the postectopic ("returning") cycle in the presence of a rather regular sinus pacemaker. Shortening of the returning cycle—observed only after ectopic P waves with short coupling—is interpreted as indicating interpolation of the parasystolic atrial beat causing prolongation of the postectopic S-A conduction time. Comparison of the sinus P-P interval with that containing an interpolated premature beat permits exact determination of the increment in S-A conduction time; the latter is found to be within the range of the delay encountered in disturbances of A-V conduction. This fact, and the absence of aberrant intra-atrial conduction of the sinus impulse after interpolation, are considered to be new evidence that the delay of S-A conduction occurs within the structure of the S-A node.

Kinetocardiographic Study of Precordial Bulges in Myocardial Infarction

John O. Langley and E. E. Eddleman, Jr., Birmingham, Alabama

One hundred and two patients with proved myocardial infarctions were studied with the kinetocardiographic technic (ultra-low frequency precordial movements). These included 60 patients with acute myocardial infarctions and 42 patients with old infarctions. Graphic records, corresponding to the V leads of the electrocardiogram and subcostal epigastric areas, were obtained on all patients. Paradoxic precordial movements, or bulges, with a duration of 0.20 second or greater

were noted in 68 per cent of the patients studied. These occurred more frequently in anterior infarctions (72 per cent) than in posterior infarctions (67 per cent). The bulge with the largest amplitude was present in the V_3 electrocardiographic position in 17 per cent of the patients, and 51 per cent of all the bulges occurred in either the V_2 or V_3 positions. When the maximum bulge occurs in the V_4 or V_6 positions, it cannot be distinguished from an exaggerated apex impulse (PMI) resulting from an increased function or hypertrophy of the left ventricle. Although the bulge cannot be solely relied upon for diagnosis of myocardial infarction, very often it is a significant help in confirming or establishing the suspected clinical diagnosis. In addition, bulges may occur before electrocardiographic or laboratory evidence of infarction and, therefore, is particularly helpful in such instances. Many bulges can be felt at the bedside, which re-emphasizes the importance and usefulness of chest-wall motions as a part of the physical examination.

Retrograde Left Ventriculography with a J-Shaped Catheter

Jerry J. Lasser, Leonard A. Steinfeld, John E. D'Aria, Murray G. Baron, Gabriel Genkins, and Alvin J. Gordon, New York, New York

Comparison was made between a standard NIH catheter and one with a J-shaped tip as to the ease of crossing the aortic valve during retrograde ventriculography in 54 children and adults with congenital and acquired heart disease.

Left ventriculography was performed with a standard NIH catheter in 27 patients. In 17 patients with normal aortic valves the left ventricle was entered in 12. In 5 cases, the aortic valve could not be passed. In 10 cases with aortic stenosis, catheterization was successful in 7.

The J catheter was employed in a second series of 27 patients. Of 24 patients with normal aortic valves, only 1 failure occurred; this was due to inability to reach the ascending aorta. In 3 patients with aortic stenosis, the left ventricle was entered in 2.

With the J catheter the normal aortic valve was passed in a greater percentage of cases. Minimal fluoroscopy time was required. Furthermore, this technic eliminates the danger of entering the coronary arteries and reduces possible trauma to the aortic valve. Arrhythmias were no more frequent and pressure pulses obtained were satisfactory.

A disadvantage of the J catheter is the possibility of interfering with mitral-valve function when the catheter is in the left ventricle. This may be obviated by proper catheter placement.

Comparison of the Recovery of Beta-Hemolytic Streptococci by Direct Plating and Mail-In Methods

Agnes Lattimer, Alan C. Siegel, and June DeCelles, Chicago, Illinois

In connection with a program for enhanced primary prevention of rheumatic fever in a large city, this study was undertaken to assess validity of a mail-in method for the inexpensive, convenient processing of throat cultures for group A β-hemolytic streptococci. A total of 1,011 throat cultures, using paired dacron swabs, were obtained from children with upper respiratory tract infections. One swab was plated immediately onto a sheep's blood agar plate and incubated, the other swab was streaked onto a filter-paper strip; both swab and filter-paper strip were mailed to the laboratory. All 3 methods were found to be accurate for the recovery of β-hemolytic streptococci, at the 86 to 89 per cent level. Filter-paper strip and swab had 7.2 per cent and 1.2 per cent respectively of cultures showing no growth. A second study of 650 cultures compared plain cotton, plain dacron, serum cotton and serum dacron swabs. The plain cotton swab was less accurate than the other 3. A third study was done using paired dacron swabs, to compare the mail-in method in different laboratories. Throat cultures were obtained from 2 sources, and the inoculated plates were independently read in 2 separate laboratories. Readings from the 2 laboratories agreed closely, and again compared favorably with the direct plating technic. Comparison of bacitracin and Lancefield methods for grouping β-hemolytic streptococci revealed that the former method detected group A strains, but 13 per cent of cultures grouped as A by bacitracin disc were Lancefield non-A. No Lancefield group A organisms were grouped as non-A by the disc. It is concluded that the dry dacron swab mail-in procedure is a valid, inexpensive, convenient method for large-scale identification of group A β-hemolytic streptococci from throat cultures.

Freedom from Cerebral-Vascular Accidents in Pharmacologically Treated "Benign" Hypertensive Disease (P)

Richard E. Lee, Arthur W. Seligmann, Melva A. Clark, and Patricia A. Rousseau, New York, New York

One hundred thirty-eight patients with grade 1 to grade 2 hypertensive disease have been followed for an average of 84 months. Initial mean blood pressure was 196/122 mm. Hg. Twenty-nine patients either were given no medication or were so inadequately treated that blood pressures failed

to fall, or gradually rose. The remaining 109 patients were treated effectively with a final blood pressure average of 162/96 mm. Hg. During the period of follow-up, 14 patients have had a "stroke." With 1 exception (a mild case with minimum blood-pressure reduction), all have occurred in the "untreated" group. The nonstroke patients' initial and final blood pressures were 198/119 mm. Hg and 162/96 mm. Hg, while the stroke patients' blood pressures were 191/122 and 236/129 mm. Hg respectively. The correlation between lowered blood pressure and absence of cerebral-vascular accident is highly significant, statistically $p<0.001$.

Injury Potential of Embryonic Cardiac Tissue

Louis Lemberg, Robert J. Boucek, and George H. Paff, Miami, Florida

The electrical and mechanical properties of the 72-hour chick-embryo heart were recorded after heat injury. The heart was isolated and placed in Tyrode solution. The sensing arm was enveloped by a heating coil that provided measured heat at the contactual tip. Ambient temperature was maintained at 30 ± 0.5 C. Surface punctate heat of 40 C. was applied for 30 seconds. Reproducible electrographic injury potentials were obtained from isolated atria ventricles and coni and from intact heart preparations.

Grading of injury on the electrocardiogram was based on a composite of measured J displacement, T-wave inversion, and U-wave prominence. Corrections were made for mass and surface area differences in the 3 chambers. The mechanical events were analyzed under the same experimental conditions. Chamber contraction was made to displace a weight of 0.5 mg. (sensing arm). The resulting myogram was measured for maximum height and degree and time duration of the slope in the initial and terminal segment of the contraction curve.

The following observations were made: (1) Irreversible injury potentials were seen only in the atrium. (2) The conal injury potentials are least intense. (3) There is some deterioration in the mechanical response to injury in all 3 chambers.

These results indicate that the atrium may have a more differentiated membrane at 72 hours of development in the chick-embryo heart. The conus has a more primitive and less differentiated membrane. Atrial and ventricular mechanical response appears to be similar at this stage of development. Conal muscle has a slow muscular contraction. The electrographic and myographic response to heat injury of the isolated chambers are strikingly similar to their counterparts in the intact heart.

Natural History of Patients with "Acyanotic" Tetralogy of Fallot

Bessie L. Lendrum, Magnus H. Agustsson, Rene A. Arcilla, Benjamin M. Gasul, and Herbert G. Mercado, Chicago, Illinois

Twenty-one patients with acyanotic tetralogy of Fallot were studied by serial phonocardiography, angiocardiography, and cardiac catheterization; 9 were recatheterized 2 to 4 years later. Seven patients were under 8 months, 5 were 8 to 24, and 9 were over 24 months of age. In all, the systemic arterial oxygen saturation was 90 per cent or over. The initial auscultatory, x-ray, and electrocardiographic findings were generally those of uncomplicated large ventricular septal defects, but with increasing age the pansystolic murmur was gradually transformed into the ejection murmur of pulmonary stenosis, the pulmonary vascularity decreased, and the electrocardiogram changed to predominant right ventricular hypertrophy. Wide splitting of the second sound (0.05 to 0.10 second) was observed in the phonocardiograms. The splitting gradually increased with age, while the intensity of the pulmonic closure diminished. Cardiac catheterization revealed left-to-right shunts at the ventricular level in all 21 patients. The following changes occurred in the group of 9 recatheterized patients: (1) The average pulmonary/systemic blood-flow ratio fell from 2.4 (range 1.1 to 4.0) to 1.3 (range 0.4 to 2.1). (2) The right ventricular pressure, which was always elevated (6 cases at systemic pressures), remained the same or increased. (3) The moderately elevated pulmonary pressures invariably fell. (4) The first angiocardiograms showed right ventricular reopacification; later, 6 showed early opacification of the aorta. All 7 young infants subsequently developed cyanosis by 1 or 2 years of age, whereas only 4 of the 14 older ones became cyanotic during 2 to 6 years of follow-up. It would thus appear that, in acyanotic infants with tetralogy of Fallot, the predominant manifestations are those of a large ventricular septal defect, but at a later age the findings of pulmonic stenosis usually predominate.

Electronic Device for Accurate Identification of the Cardiac Conduction System: Its Use in Open-Heart Surgery (P)

Derward Lepley, Jr., William Bormes, and Kenneth L. Kayser, Milwaukee, Wisconsin

Surgically induced complete heart block has been a serious complication of open-heart surgery. This report describes an electronic device that identifies the A-V node and the bundle of His through a measurable difference in impedance to the flow of a minute electrical current in these

structures. The impedance is measured through a gold 3-pole probe constructed in such a manner that the surface interference is reduced and the cardiac conduction system may be accurately detected within 1 mm. The probe will locate the conduction system to a depth of 3 mm. from the endocardial surface. The change in impedance detected by the probe is transmitted to a transistorized unit consisting of an oscillator with a frequency of 50 Kc. per second, impedance bridge, and power source. Changes in impedance are signaled by a speaker emitting a tone of changing pitch.

The probe, which is 4 mm. in diameter, is autoclaved and used in the open heart. Accuracy within 1 mm. has been repeatedly demonstrated in animal experiments. No damage to cardiac tissues has been demonstrated from the 0.1 ma. current employed.

To date, 15 patients, in whom heart block would be an expected complication, (i.e., large ventricular septal defect, tetralogy of Fallot, and A-V canal) have been operated upon using this instrument. Accurate localization of the conduction system was achieved in all 15 patients and heart block occurred in none. It would appear that this method may materially reduce the incidence of surgically induced heart block.

Effect of Respiration on Cardiac Murmurs: An Auscultatory Illusion

Hugh S. Levin, Vincent Runco, Charles F. Wooley, and Joseph M. Ryan, Columbus, Ohio

In evaluating the significance and origin of cardiac murmurs, intensity change during respiration is commonly considered an important physical finding. In an attempt to evaluate the reliability of this sign, 8 patients with congenital heart disease and 2 with acquired heart disease were studied.

Right-sided murmurs were recorded simultaneously from the chest and from their point of origin within the heart with an Allard-Laurens micromanometer. The intensity of the murmur internally and externally during deep inspiration and expiration was evaluated by auscultation and by phonocardiographic recording. Systolic ejection murmurs were studied in 7 cases, pulmonic diastolic murmur in 2, and a continuous murmur in 1.

In 7 patients the behavior of the intracardiac murmur failed to parallel the behavior of the murmur heard externally, which was less intense during deep inspiration than during deep expiration. Paradoxically, the murmur in the heart remained unchanged with these 2 respiratory maneuvers in 4 of the 7 patients, and in 3 of the 7 it was actually louder on inspiration than on expiration. It is concluded that the behavior of a murmur on the chest during deep inspiration and expiration is in most cases a poor reflection of its behavior in the heart, probably because of the variable amount of inflated lung interposed between the heart and the chest wall under these circumstances. Conclusions concerning variations of blood flow based on external murmur changes during deep breathing may therefore be unreliable.

Intracardiac Phonocardiography in Organic Pulmonic Insufficiency

Hugh S. Levin, Vincent Runco, Charles F. Wooley, and Joseph M. Ryan, Columbus, Ohio

Organic pulmonic valvular insufficiency is a rare affection, difficult to recognize clinically. A hemodynamic explanation for the unusual murmur encountered in this disease has not been clearly elucidated.

The present report concerns the evaluation of 3 patients: the first, with isolated pulmonic insufficiency 5 years after staphylococcal endocarditis; a second, aged 72, with isolated pulmonic insufficiency of undetermined etiology; and a third with organic pulmonic insufficiency in addition to a patent ductus arteriosus. Each patient had a coarse diamond-shaped, early diastolic, left sternal-border murmur. An Allard-Laurens intracardiac micromanometer was used for simultaneous intracardiac pressure and sound recording, while the murmur was registered concurrently from the chest with a conventional phonocardiogram.

The diagnosis of organic pulmonic insufficiency was established by similar pulmonary-artery and right ventricular end-diastolic pressures and by localization of the diastolic murmur to the main pulmonary artery and right ventricular outflow tract. It was further substantiated by cineangiography once. This diamond-shaped murmur, loudest just proximal to the pulmonic valve, corresponded in timing and configuration to that recorded from the chest. In early diastole, coincident with the occurrence of the murmur, the right ventricular pressure dips significantly below the pulmonary-artery pressure for a brief period and affords a plausible hemodynamic explanation for the crescendo-decrescendo nature and early diastolic timing of the characteristic murmur of organic pulmonic insufficiency. Intracardiac phonocardiography thus appears to be a valuable tool in the detection and study of this unusual defect.

Cardiac Complications of Cerebral Arteriovenous Fistula in Infancy (P)

O. Robert Levine, A. Gregory Jameson, Gerhard Nellhaus, and Arnold P. Gold, New York, New York

Four infants with congenital arteriovenous malformation of the vein of Galen were studied; in each there was clinical evidence of cardiac involvement secondary to the arteriovenous shunt. The first was a neonate who died in severe circulatory failure without evidence of neurologic disease. The second underwent cardiovascular studies pre- and postoperatively. The shunt was demonstrated by a marked elevation of oxygen saturation in internal jugular venous blood as compared with iliac venous blood; this discrepancy was markedly diminished after operation. Cardiac output was measured by the dye-dilution technic, and postoperatively showed a 50 per cent decrease as compared with the preoperative determination. The third child presented during infancy with roentgenographic evidence of cardiomegaly secondary to cerebral arteriovenous fistula. Serial chest roentgenograms showed a decrease in the size of the cardiac image after reduction of the fistula, and further return of heart size toward normal after its complete extirpation. The fourth underwent operation for complete removal of a cerebral arteriovenous aneurysm, and succumbed 2 days postoperatively with clinical evidence of circulatory overload.

The hemodynamic effects of arteriovenous fistula are shown. The precise mechanisms responsible for the compensatory increase in blood volume and cardiac output are incompletely understood. Phlebotomy in the presence of circulatory congestion secondary to a large shunt should be avoided, since it may deprive the patient of a valuable homeostatic response. Digitalis is indicated if myocardial failure contributes to circulatory congestion. Closure of an arteriovenous fistula results in abrupt loading of the left heart. The administration of excessive quantities of fluid and blood should be guarded against during and immediately after operation.

Effect of Exercise on the Blood Volume of the Lung and Left Heart in Man

Gilbert E. Levinson, Martin J. Frank, Robert S. Palman, Ernest N. Landy, and Alberto Behar, Jersey City, New Jersey

Studies of the effect of exercise on cardiopulmonary blood volume have given conflicting results, probably due chiefly to the use of peripheral arterial dilution curves to calculate "central" volumes. In the present study, the volume of the lungs and left heart (LLHV) was measured from curves recorded from the aortic root after pulmonary artery injection, in 2 normal subjects and 17 patients with valvular heart disease, during rest and bicycle ergometer exercise in the supine position.

Mild exercise (5 subjects) caused mean increases of 33, 22, and 13 per cent in oxygen consumption, heart rate, and cardiac output respectively, and no change in LLHV.

With moderate exercise (103 per cent mean increase in O_2 consumption), 5 subjects without cardiac output response (mean change = + 1 per cent) had an insignificant (5 per cent) mean fall in LLHV. However, in 9 subjects with output increases of 27 to 111 per cent, there was a significant ($p < 0.005$) mean increase of 31 per cent in LLHV. Mean increase in LLHV was 71 per cent when output increase was mediated chiefly by stroke volume and 31 per cent when output increase was due chiefly to tachycardia.

For the 19 subjects, LLHV change correlated well ($r = 0.69$) with output change, but better ($r = 0.83$) with change in stroke volume.

These results demonstrate that cardiopulmonary blood volume expands when output increases with exercise and suggest that the volume expansion may be intimately involved in the presence and magnitude of a stroke-volume response to exercise.

Afterload as an Independent Determinant of Myocardial Contractility (P)

Matthew N. Levy, Elias S. Imperial,† and Harrison Zieske, Jr., Cleveland, Ohio

In the canine, isolated, left ventricle preparation, the outflow resistance could be augmented instantaneously by means of a solenoid valve. Phasic left atrial and ventricular pressures and aortic flow were recorded, and analogue computer elements were employed to register ventricular power, stroke volume, and stroke work simultaneously. The solenoid valve was actuated at random at various phases of the cardiac cycle for a duration slightly longer than 1 cardiac cycle. When the valve was closed during diastole, the ventricle began its next contraction under initial conditions identical to control. The increased resistance evoked by solenoid closure elicited a more gradual decline of aortic pressure. When the valve was closed late in diastole, there was little change in aortic diastolic pressure. When resistance was augmented early in diastole, however, diastolic pressure was appreciably elevated. For any given outflow resistance, systolic pressure developed by the ventricle was directly and linearly related to the level of aortic diastolic pressure at the end of the preceding cardiac cycle. Furthermore, for any given diastolic pressure, the peak ventricular systolic pressure was directly related to the magnitude of the outflow resistance. Since the contraction immediately after the institution of increased resistance began from the control myocardial fiber length, and since aortic diastolic pressure and

peripheral resistance are both components of the ventricular afterload, it follows that the afterload is an independent determinant of myocardial tension development.

Surgical Treatment of Congenital Aortic Stenosis Using Cardiopulmonary Bypass: Including Methods for Preoperative Diagnosis of Types

Morris J. Levy, Richard L. Varco, Yang Wang, Paul Adams, Jr., Ray C. Anderson, and C. Walton Lillehei, Minneapolis, Minnesota.

Considerable improvement has been made in preoperative evaluation and 4 different types of stenosis are described: valvular, subvalvular, supravalvular, and mixed. The use of cardiopulmonary bypass with cardiac arrest has been made a satisfactory correction of all types possible with a reasonable rate of mortality.

The report included 34 operated patients aged from 5 months to 24 years. Criteria for congenital etiology have been applied. The diagnosis was made by the presence of physical findings typical for aortic stenosis. Left-heart catheterization with selective angiography was helpful in distinguishing between the different types. The series includes: isolated valvular stenosis, 25 patients; subvalvular, 5; supravalvular, 2; and mixed (valvular plus subvalvular), 2. The preoperative maximum systolic gradient across the obstruction varied from 45 mm. to 230 mm. Hg with an average of 95 mm. Hg. The operative technic concerning the different types is emphasized. The total-body perfusion has changed from normothermic to moderate hypothermic levels. The cardiac arrest in the last 19 operations was achieved by profound selective cardiac hypothermia. The mortality was 12 per cent with 1 fatal case among the last 26 operations. The other 3 deaths were: 2 in infants, 7 and 8 months of age respectively, both associated with extensive endocardial fibroelastosis. The third was in an uncorrectable case with hypoplastic left ventricle and aorta. The results showed that the average postoperative maximum systolic gradient dropped to 18 mm. Hg. The average size of stenotic orifice measured 7 mm. in diameter and was extended to 18 mm. The systolic thrill disappeared in 74 per cent and the systolic murmur was abolished or decreased to a substantial degree. The future outlook for some valvular involvement is discussed. Once a significant stenosis is present, it is our opinion that surgical correction is imperative unless compelling contraindications exist. The disease in infants is frequently associated with additional anomalies. Left-heart catheterization is required for preoperative evaluation.

Coronary Visualization: Indications and Clinical Correlation

William Likoff, J. Stauffer Lehman, Hratch Kasparian, and Alan Kramer, Philadelphia, Pennsylvania

Recent advances in technic permit the coronary arterial circulation to be visualized quite routinely by means of opaque radiographic material. A correlation of this type of examination with the clinical patterns of patients known to have advanced atherosclerosis has been carried out in order to clarify its safety, its diagnostic usefulness, and whether or not this form of examination can be of assistance in acute and chronic treatment.

The safety of the procedure was indicated by the fact that not a single mortality or serious morbidity occurred in 100 separate procedures.

Coronary arteriography appeared to have diagnostic limitations. In discrete instances immediately preceding the occurrence of a myocardial infarction, coronary visualization appeared to be normal. This also was observed in patients with longstanding and serious electrocardiographic abnormalities.

The ability to visualize extensive collateral channels circumventing an occluded area or the demonstration of a recanalization of a known previously occluded arterial segment was accepted as a favorable sign. In many instances, however, these findings were not demonstrated in patients who had enjoyed full and long recoveries from a coronary occlusion.

The explanation for the paradoxes indicated above may rest with the improved technics of examination. However, coronary arteriography represents an important safe diagnostic tool.

Acute Myocardial Infarction Patterns in Young Subjects with Normal Coronary Arteriograms (P)

William Likoff, Bernard L. Segal, and Leonard S. Dreifus, Philadelphia, Pennsylvania

The electrocardiographic pattern of myocardial infarction has been encountered in 6 male patients between 16 and 21 years of age. These abnormal patterns were equally divided between anterior and posterior myocardial involvement.

These patients were asymptomatic and presented with a Grade I to II ejection systolic murmur heard best at the third and fourth left interspaces.

Because of the unusual electrocardiographic abnormalities in this age group, coronary arteriography was performed in each individual. The visualization of the coronary vessels was normal without exception. There was no evidence of anomalous coronary vessels.

The clinical survey failed to reveal the etiology of these acute myocardial infarction patterns. It is postulated that defects in intraventricular conduction with abnormal ventricular repolarization owing to remote myocarditis may have resulted in the electrocardiographic abnormalities.

These experiences suggest that the pattern of an acute myocardial infarction in young subjects may occur with normal patency of the coronary arteries. This realization materially affects the prognosis and therapeutic approach to the problem.

Resection of Chronic Postinfarction Myocardial Aneurysms Using Temporary Cardiopulmonary Bypass

C. Walton Lillehei, Minneapolis, Minnesota, Herbert E. Warden, Morgantown, West Virginia, Richard A. DeWall, and Morris J. Levy, Minneapolis, Minnesota*

A myocardial aneurysm resulting from coronary occlusion is not a rare pathologic entity. The incidence varies between 8 and 20 per cent of all myocardial infarcts. This condition is clinically diagnosable. The prognosis has been grave with a mortality above 70 per cent in the 3 years after the initial infarct. The most frequent cause of death has been congestive heart failure. Sudden death from systemic embolism has been second in frequency. The disease is surgically curable, and the operative procedure and postoperative course have been surprisingly well-tolerated by the patients.

The report consists of 5 patients, all male, aged 47 to 63 years. The time lapse between the initial infarct and the appearance of the left ventricular aneurysm was 2 weeks to 2 years. The time interval between the initial infarct and surgery was 5 months to 6 years. Inadequate bedrest after the infarct occurred in 1 patient. One patient experienced a systemic embolus prior to surgery and 2 had systemic hypertension. The diagnosis was suggested by chest x-rays and ECG tracings, supported by kymogram and confirmed by angiography. Right-heart catheterization showed reduced cardiac output and elevated pulmonary pressures. A method of achieving cardiopulmonary bypass, utilized in all patients, was developed. The surgery consisted of radical excision of the sac followed by ventriculoplasty. A high incidence of mural thrombi, as well as pericardial obliteration, was present. The anatomic distribution of the aneurysm, as well as the histopathology of the specimen, was studied. All patients survived and follow-up from 6 months to 36 months after operation included postoperative hemodynamic data. There have been no late deaths to date.

More attention should be given to this relatively common postinfarct complication because excision under bypass technic is a rational approach.

Hypocholesterolemic Agents: A Comparative Study

Philip Lisan, Wilbur Oaks, Sheldon R. Bender, and John H. Moyer, Philadelphia, Pennsylvania

The 3 major methods of reducing serum cholesterol are: (1) inhibition of absorption of cholesterol from the gastrointestinal tract, (2) enzyme inhibition of endogenously synthesized cholesterol, and (3) increase in metabolic breakdown of cholesterol.

In the first category, low fat diet, linoleic and linolenic acids, and bile-sequestering agents were utilized. The low fat diet and linolenic acid compounds lowered serum cholesterol in about 50 per cent of the patients (15), with a mean depression of 54 mg. per cent. The disadvantages are unpalatability, expense, and escape from the hypocholesterolemic properties after 4 months. The bile-sequestering agents were unpalatable and of no value.

The second group is characterized by triparanol, 250 mg. daily, which inhibits the endogenous synthesis of cholesterol by blocking the conversion of desmosterol to cholesterol. Triparanol was effective in 85 per cent of the patients (100) and produced a mean serum-cholesterol depression of 75 mg. per cent. No clinical side effects were noted and no significant changes in liver function (bromosulfphalein) were found.

In doses of 1 to 2 Gm., nicotinic acid lowered serum cholesterol in 9 of 13 patients with a mean depression of 55 mg. per cent. Objections to the use of this drug are the following side effects: flushing and itching (6), angina (2), anorexia (2), and gastrointestinal bleeding (1).

d-Thyroxine, 6 mg. per day, has the property of lowering cholesterol without the usual associated hypermetabolic state produced by other thyroid analogues. The serum cholesterol was lowered in 9 of 10 patients with a mean serum-cholesterol depression of 54 mg. per cent. All patients had angina prior to therapy and 2 patients had an increase in severity and frequency of angina. There is also a possibility that an escape mechanism may occur while on *d*-thyroxine.

Combination therapy may be of value in refractory cases and in this series 250 mg. triparanol and 1 Gm. nicotinic acid were used with beneficial results in 9 of 10 patients, with a mean serum cholesterol depression of 46 mg. per cent. It was also found that a high fat diet will elevate the serum cholesterol previously depressed by triparanol, but an increase in dosage from 250 mg. to 500 mg. re-established the initial cholesterol depression.

Miscellaneous agents such as fat enzymes, proteolytic enzymes, and cortical catalysts were found to be of little value in lowering serum cholesterol.

Three-Year Study of Triparanol

Philip Lisan, Wilbur Oaks, and John H. Moyer, Philadelphia, Pennsylvania

This is a clinical study of 21 patients with coronary artery disease who were followed continuously on triparanol for periods of 24 to 36 months. There was a significant and persistant fall (38 mg. per cent, with $p = < 0.001$) in 18 (85 per cent) of these patients during the 2- to 3-year study. There was no clinical evidence of toxicity. Liver-function studies showed no impairment of function (bromosulphalein) even at the 3-year period. Renal and hematologic parameters remained unchanged and within normal limits. Other fat studies, such as serum triglycerides, unesterified fatty acids, and lipoproteins, could not be correlated with the reduction in cholesterol.

There were 23 patients in the orginal series but 2 patients died of coronary thrombosis with myocardial infarction at 12 and 14 months. Only 1 patient (of 21) had another coronary thrombosis, also at 12 months, but survived and now has reached 24 months. Subjectively the patients had diminution in frequency and severity of angina pectoris and intermittent claudication.

There was no manifestation of any estrogenic effects nor any evidence of adrenal insufficiency. If anything, there was a mild euphoric response. Triparanol did not appear to affect the blood coagulation nor the prothrombin activity, especially in those patients who were on anticoagulant therapy.

Effect of Acute Normovolemic Anemia on Pulmonary Arterial Pressure

J. Maxwell Little, J. Richard R. Bobb, Ward Huffman, and Emily A. Angell, Winston-Salem, North Carolina

The effect of acute normovolemic anemia on pulmonary arterial pressures (PP) has been studied in 2 series of dogs under chloralose anesthesia: a control group (9 dogs) with comparable anesthesia time and a group of 8 anemic dogs. After control measurements (3 to 16 per dog) of PP, cardiac output (Fick principle), hematocrit, and blood volume, the experimental group was bled 100 ml. at 10-minute intervals, immediately replacing the volume with 6 per cent Dextran. The final hematocrit range was 7.5 to 14.9 per cent. PP measurements (3 to 7) and the other measurements were repeated. The dogs breathed 100 per cent oxygen during all measurements. Changes in blood volume, stroke volume, and mean arterial pressure were not significant in either series. There were significant increases in mean central venous pressure, cardiac output, and heart rate in the anemia series. Four of 9 control dogs had a significant ($p < 0.05$) increase in mean PP, range 1.7 to 3.9 mm. Hg, and 1 had a significant decrease for a net increase of means of 6 per cent. In 7 of 8 anemic dogs, mean PP increased ($p < 0.05$), range 2.2 to 8.1, for a net increase of means of 45 per cent. The respective net changes in pulmonary resistance, were +50 per cent for control and —28 per cent for anemia dogs. Pulmonary systolic pressure increased ($p < 0.05$) in 3 of 7 control and in 6 of 8 anemia dogs (respective ranges being 2.6 to 6.2, and 10.6 to 18.9 mm. Hg). Pulmonary diastolic pressure increased ($p < 0.05$) in 1 of 7 control and in 1 of 8 anemia dogs. There was no relation between the changes in cardiac output and in mean PP in either series.

Use of Intracardiac and Intravascular Phonocardiography in the Diagnosis of Congenital Heart Disease

Chi Kong Liu, Ronald T. Piccirillo, Torrance, California, and Frederick Kellogg, Long Beach, California

Intracardiac and intravascular phonocardiography has been used in conjunction with pressure curves obtained in cardiac and vascular catheterization since 1958. It has been shown that heart sounds may be produced by movement of a cardiac catheter within the heart causing undesirable artifacts. This paper emphasizes the value of intracardiac and intravascular phonocardiography in the diagnosis of congenital heart disease and means of avoiding artifacts.

This study included 72 cases of congenital heart disease. The recording of a diastolic murmur near the pulmonic valve with greater intensity in the outflow tract of the right ventricle indicates pulmonary regurgitation. Since the normal pulmonary diastolic pressure is low, a definite diagnosis of pulmonary regurgitation by pressure measurements cannot be made unless it is almost identical to that of the right ventricle.

Retrograde aortic catheterization is useful in localizing the site of a coarctation by the decrease or disappearance of the intravascular murmur proximal to the lesion. By this method 1 case of abdominal coarctation was verified. A systolic murmur just distal to the aortic or pulmonary valve, without a systolic pressure gradient across these valves or evidence of shunt in the latter, probably indicates a nonsignificant aortic or pulmonary stenosis or an innocent flow murmur.

To reduce internal artifacts, undue looping or tension of the catheter should be avoided. Externally, one should avoid touching the catheter, the table, or the pressure gauge.

Anatomical Basis of Hypertension

Harry Lobel, Omaha, Nebraska

Because the arterial system has been studied for thousands of years, search for new anatomic structures seems futile. Nevertheless, healthy arteries were examined and many features for the prevention of hypertension were discovered.

The most obvious of these features is the structure and design of the points of arterial bifurcation. At the mouths of arteries branching from the aorta are funnel-shaped nozzles. These face upstream like Pitot tubes. Microscopic examination reveals that some of the nozzles have muscle fibers. On stimulation, the renal artery, for example, is seen to adjust its contour to streamline varying flows of blood. Malfunction, such as that due to dystrophy of the muscle fibers, results in hypertensive pressure.

Dynamic models show that, when the contour of these nozzles corresponds with the rate of acceleration of the fluid, a minimum of pressure results in a given flow. But when the contour is distorted, a hypertensive pressure is necessary for the same volume of flow.

When the models are distorted, there are 2 kinds of pressure: one is an effective pressure that does work by overcoming resistance; the other is a useless back-pressure. This back-pressure is due to a "reactive," as differentiated from a resistive force. The vector sum of these 2 types of pressures, is the "impedance."

The reactive component of impedance should not be taken lightly; it lowers efficiency and contributes to stress and, when it reaches a critical value, results in hypertension.

Subtle Roentgenographic Findings in Early Left-Heart Failure (P)

R. Bruce Logue, James D. Rogers, and Britt B. Gay, Atlanta, Georgia

The recognition of the early manifestations of congestive heart failure is essential if therapy is to be instituted at a time of optimum effectiveness. The presence of pulmonary congestion resulting from stenosis or left ventricular failure produces a variety of symptoms and signs; however, the detection of characteristic changes in the x-ray may at times offer the initial or only clues to its recognition. These findings may be present in the absence of cardiac enlargement, ventricular diastolic gallop rhythm, pulmonary rales, peripheral venous distention, hepatomegaly, or edema. Such nonspecific symptoms as weakness, insomnia, restlessness, extrasystoles, unaccountable fatigue, or cough may be the presenting complaints. The following roentgenographic findings may be clues to early pulmonary congestion: (1) distended pulmonary veins; (2) poor definition of the hilar structures; (3) increased intersitial density of the lungs resulting in poor definition of the pulmonary vessels, (4) costophrenic septal lines; and (5) minimal pleural effusion. In a review of 100 cases of interstitial pulmonary edema admitted to Emory University Hospital, the initial suspicion of pulmonary congestion was noted in 20 per cent in the conventional x-ray study. Serial x-ray films and, in selected instances, tomograms were taken to demonstrate changes with therapy.

In patients with a basis for heart failure, signs and symptoms that may be readily overlooked may become meaningful in the presence of the early signs of interstitial edema in the chest roentgenogram.

Correlation of Electrocardiographic Findings Before and After Surgical Repair of Persistent Common Atrioventricular Canal

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The characteristic electrocardiographic and vectorcardiographic features present in persistent common atrioventricular (A-V) canal defect have been described by various authors. The most important diagnostic feature is the QRS vector in the frontal plane, which is directed counterclockwise with the main mass above zero.

Conflicting electrophysiologic bases for this alteration in excitation of the QRS complex have been advanced.

Since surgical correction would allow cardiac chamber size to return toward normal, but not influence the conduction system, correlation of electrocardiographic findings before and after surgical repair could help to define the problem.

Among the patients with persistent A-V canal treated surgically at the University of Minnesota, 10 have had preoperative and also normal postoperative physiologic data and formed the basis for electrocardiographic correlations.

The characteristic QRS loop in the frontal plane was present in each patient preoperatively and was unchanged postoperatively.

The other electrocardiographic features frequently present: horizontal QRS, vector, biventricular hypertrophy in the precordial leads, rSR pattern in lead V_1 and P-wave abnormalities, all tended to return toward normal.

This study suggests that, while the degree of cardiac dilatation and/or hypertrophy influences these latter findings, the characteristic frontal plane QRS vector appears related not to chamber size or hypertrophy but rather to elongation and abnormal location of the conduction tissue, specifically a dorsoinferior displacement of the conduction tissue as seen in forms of persistent common A-V canal.

Blood Supply to Cardiac Conduction Tissue in Pig and Man

George D. Lumb and Henry P. Singletary, Wilmington, North Carolina

Most cardiac experimental work is performed in dogs. Differences from human coronary blood supply exist in this animal. Dissection and perfusion in experimental animals showed 2 similar principal arteries supplying the conduction tissue in man and pig: anterior, from anterior descending artery; posterior, from end of right coronary artery at origin of posterior descending artery. Therefore, these experiments were performed using pigs. Anterior septal ligations in 10 pigs produced small localized infarcts in the anterior part of the interventricular septum inferior to the distal part of the bundle of His. Ligation in 16 pigs of the terminal part of the right coronary artery immediately before the origin of the posterior descending, or of the posterior septal itself, caused: death within 6 hours with preceding complete heart block in 6 but no evidence of heart block in 3; survival with infarct involving the upper two-thirds of the interventricular septum posteriorly, tapering anteriorly to involve the upper one-sixth in 7. In 4 of these the AV node and bundle of His showed partial destruction, while in the remainder no necrosis was observed. Perfusion with various materials demonstrated communications between anterior and posterior vessels. Ligations, however, indicate that the posterior vessel provides the major blood supply to conduction tissue. Sparing of conduction tissue in some cases when the posterior vessel is ligated is being studied. Vascular communications are possible from the anterior septal artery, from terminal branches of the left circumflex artery, and from arterial vessels. It is thought that these results are significant, as blood supply to conduction tissue in the pig resembles closely the arrangement in humans.

Distribution of Blood Flow in the Canine and Human Heart (P)

Lloyd D. MacLean, Young Song Kim, and Paul H. Hedenstrom, St. Paul, Minnesota

A method for determining the functional anatomy of the vascular system of the heart using radioactive microspheres of uniform size has been developed. The method has been used, in vivo, in 130 dogs and is suitable for postmortem examination of human hearts, which have been studied in 50 instances. Microspheres either 20 or 50 μ in diameter were injected into the coronary system from a perfusion flask delivering a measurable blood flow at a known and physiologic pressure. Spheres of 20 μ were small enough to pass through all intercoronary anastomoses and all arteriovenous shunts except capillaries so that the radioactivity of the tissue proved to be a measure of tissue capillary flow as confirmed by a second method. In all experiments the venous outflow was collected and radioactivity determined from which total flow through arteriovenous shunts was calculated. The hearts were divided into anatomic parts, the radioactivity determined, and tissue capillary flow calculated. Perfusion of hearts with coronary occlusion permitted quantitation of flow via interarterial anastomoses. The results revealed: (1) Approximately 3 per cent of total coronary flow passes through arteriovenous shunts in both dog and man. (2) Between 1 and 9 per cent of normal flow passes via interarterial shunts greater than capillary size into the distribution of the anterior descending coronary artery when this vessel is occluded, in the dog. (3) Intercoronary anastomoses 50 μ or greater in diameter are present in human hearts in all age groups. Collateral circulation is increased by severe coronary sclerosis but not by age alone. (4) Arterioluminal or arteriosinusiodal communications to the left ventricular chamber were not demonstrated in human hearts.

Renal Handling of Serum Nonesterified Fatty Acids, Triglyceride, and Cholesterol in Diuresing Subjects

Joseph H. Magee, Allan L. Forbes, Richmond, Virginia, and W. Parker Anslow, Charlottesville, Virginia

Previous studies showed renal extraction of serum nonesterified fatty acids (NEFA) in the fasting water-diuresing subject with hypertensive or urologic disease. Investigation was continued in 15 similar subjects, superimposing solute diuresis, after infusion of 100 Gm. mannitol (M), on existing water diuresis. Mean right renal extraction of NEFA was 0.100 mEq./L. prior to M, with standard deviation (σ) of 0.350 mEq./L.; following M, mean extraction was abolished (0.005 mEq./L.) with σ of 0.017 mEq./L., lacking statistical significance ($p > 0.5$). Directional changes in individual cases suggested reciprocity of NEFA

extraction with triglyceride output; for group, mean triglyceride output 3.5 mg./100 ml. before and 2.6 after M, a change lacking statistical significance ($p > 0.5$). In contrast to NEFA and triglyceride behavior, no instance of arterial-venous cholesterol differences in excess of error of replicates occurred in the same 30 paired bloods. As pointed out by Gordon, small NEFA extraction (0.050 mEq./L.) would be compatible with renal NEFA oxidation as the primary source of renal energy requirements. The role of excretion as urinary acyl conjugates and of removal by renal lymph has not been ascertained. Fluctuations of the right renal venous NEFA and triglyceride encountered respective to arterial concentration suggested active lipogenesis and lipolysis by intrinsic renal parenchymal or adipose tissue.

Gradual Improvement in Renal Blood Flow Accompanying Reduction of Blood Pressure in Human Hypertension

Joseph H. Magee, Richmond, Virignia, Allan M. Unger, San Francisco, California, and David W. Richardson, Richmond, Virginia

Renal blood flow and glomerular filtration rate have been estimated in 85 male patients, ranging in age from 28 to 67, admitted to the Veterans Administration Cooperative Study of Antihypertensive Agents with diastolic pressure averaging more than 90 mm. Hg. Forty-four have been restudied, using similar inulin and PAH clearance technies after 1 year, 23 after 2 years, 17 after 3 years, and 6 after 4 years of treatment with hypotensive drugs or placebos assigned in random, double-blind fashion. Thirty-five patients have died, including 11/12 of those whose pretreatment inulin clearance (C_{IN}) was less than 50 ml./min./1.73M.^{2} (B.U.N. over 25 mg. per cent).

After 1 year, no relation between change in blood pressure and change in inulin or PAH clearances was observed. Even with reduction in diastolic pressure of more than 15 mm. Hg sustained for more than 2 years, inulin clearance was unchanged in 14 and decreased by 10 per cent or more in 8 of 25 studies. Unchanged or increased blood pressure during the 2- to 4-year period was usually accompanied by decrease in both inulin and PAH clearances. After 24 months of treatment, there was a slight inverse correlation between blood pressure and effective renal plasma flow (C_{PAH}). When third and fourth year values were added, negative correlation between C_{PAH} and systolic ($r = -0.37$; $p < 0.01$) and diastolic ($r = -0.43$; $p < 0.01$) pressure was observed, reduction in blood pressure by more than 15 mm. Hg being associated with increase in C_{PAH}, and increase in blood pressure with fall in PAH clearance.

Though a sustained reduction in blood pressure may improve renal blood flow in hypertensive humans, improvement in glomerular filtration was not demonstrated.

Indications for Pulmonary-Artery Banding

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A variety of anomalies have, as a common denominator, excessive pulmonary blood flow and pulmonary hypertension. These are commonly associated with changes in smaller pulmonary vessels which are considered to be reversible. Banding of the pulmonary artery has as its primary objective reduction in pulmonary blood flow and lowering of pulmonary-artery pressure.

A group of cases demonstrating the variety of anomalies amenable to banding and the physiologic responses have been studied. Case 1 demonstrated the dramatic response to banding in a critically ill infant with ventricular septal defect and pulmonary hypertension, and the ability of this desperately ill infant to survive this type of temporizing surgery. Case 2 underwent resection of a coaretation and division of patent ductus arteriosus at 6 weeks of age because of chronic congestive failure. Failure persisted postoperatively in the presence of a ventricular septal defect. Banding was carried out 4 weeks later with control of the congestive failure. Case 3 illustrated the prompt improvement obtained in an infant with severe congestive failure in the presence of truncus arteriosus and pulmonary hypertension. Case 4 showed the response to banding in corrected transposition, and case 5 illustrated the response to concomitant banding in ventricular septal defect after division of a large patent ductus arteriosus. There were no deaths in this group and all patients responded satisfactorily with control of congestive failure and a return toward normal growth and development.

Pulmonary-artery banding has proved to be a safe and effective method of controlling congestive failure and reducing pulmonary hypertension in a variety of congenital cardiac malformations.

Serum-Enzyme Levels after Acute Arterial Occlusion of Dog Limbs (P)

Ugo Manzoli, Raymond Penneys, Leonard J. Feinberg, and Samuel Bellet, Philadelphia, Pennsylvania

These experiments were done to relate levels of the serum enzymes, glutamic oxalacetic transaminase (G.O.T.), isocitric dehydrogenase

(I.C.D.), and lactic dehydrogenase (L.D.H.), to ischemia of the animal limb, in the same manner that they have been related to ischemia of the myocardium. Embolism of a hind limb was produced in 16 dogs by the injection of a lycopodium suspension into the femoral artery. This resulted in severe, ischemic damage to the limb, progressing to gangrene in 13 of the 16 animals. All 3 enzymes increased within 4 hours after embolization, much before the appearance of gangrene, and remained so during the 96- to 144-hour observation period. The greatest increase was in G.O.T., the average value of which rose from approximately 40 units before embolization, to 1,000 units, at 24 to 48 hours after embolization. The next greatest increase was in I.C.D., and the least was in L.D.H. Sham operations on 4 dogs produced no significant rise in enzyme levels, nor did temporary occlusion of the femoral artery done in 12 dogs, hence embolization, per se, was responsible for the increase in serum enzymes.

Levels of these serum enzymes, then, are related to the degree of ischemic damage of the limb. Such enzyme changes probably reflect the degree of damage of the deeper tissues of the limb, something not provided by the routine clinical examinations, and should therefore be of value in the management of patients having acute, severe peripheral arterial obstructions.

Influence of the Ventriculotomy Site on the Contraction and Function of the Right Ventricle (P)

Harold W. March, Palo Alto, California, Keith Ross, London, England, Frank Gerbode, and William L. Weirich, San Francisco, California

The influence of the site of ventriculotomy on right ventricular contraction in canine hearts was evaluated by high speed photography and by ventricular function curves. The camera was a 16 mm. Wollensak-Fastax operating at 800 to 1500 frames per second. Ventricular function curves relating right ventricular stroke work to the mean filling pressure in the right atrium were constructed in the manner described by Sarnoff.

Observations in 17 animals indicate that right ventricular contraction is sequential, beginning at the apex. Early in systole the outflow tract bulges as blood is ejected into the pulmonary artery. It is maximally contracted late in systole and appears to relax later than the main right ventricular chamber.

After conventional vertical ventriculotomies paralleling the interventricular groove, adverse effects on the mobility of the entire right ventricle and on the behavior of the outflow region were observed in 8 animals. Alternatively, ventriculotomies were oriented horizontally along the axis of circumferentially shortening muscle fibers in 6 animals and in these the features of normal contraction remained unimpaired.

Ventricular function curves were constructed in 14 other animals before and after vertical and horizontal ventriculotomies. Long vertical incisions profoundly depressed ventricular function, whereas the function curves were essentially unimpaired after horizontal incisions.

It is concluded that horizontal ventriculotomy is superior to vertical ventriculotomy in that it preserves the contractile and functional characteristics of the right ventricle.

Effect of Reserpine on Circulating Catecholamines and on Hemodynamic Responses to Infused Norepinephrine

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Cardiac output (COP) (dye-dilution technic), arterial plasma norepinephrine (NE) (trihydroxyindole method of von Euler), and 24-hour urinary vanilmandelic acid (VMA) excretion (colorimetric method of Sandler and Ruthven) were measured in 33 labile hypertensives, 16 of whom were studied 4 hours after 2.5 mg. I.M. reserpine.

Reserpine did not affect arterial NE levels (0.29 ± 0.11 to 0.23 ± 0.27 μg./L.) or VMA excretion (7.76 ± 1.90 to 6.85 ± 1.86 mg./24 hours) when compared to control levels the preceding day.

Although mean blood pressure (MBP) and arterial NE rose equally in both control and reserpine-treated groups during a 10-minute 7.6 μg./min. NE infusion, there was a greater fall in COP (control −0.42; treated −0.07 L./min.) and a slightly greater rise in total peripheral resistance (TPR) (control +236; treated +143 dynes sec. $cm.^{-5}$) in the control group.

Increasing the NE infusion rate to 14 μg./min. produced a further equal rise in MBP and arterial NE levels. COP rose in both groups (control +0.81; treated +0.42 L./min.), while TRP fell in the controls (−87 dynes sec. cm^{-5}) and rose in the experimental group (+40 dynes sec. $cm.^{-5}$).

COP fell, TPR and arterial NE rose comparably during a 60-degree head-up tilt in 5 controls and 7 additional reserpine-treated patients. Infused NE while tilted exaggerated these responses and failed to prevent syncope in 2 other subjects after reserpine.

Reserpine produced no detectable changes in circulating catecholamines or urinary VMA and no significant alteration in hemodynamic responses to infused NE.

Effect of Estrogen Therapy on Interlipid Relationships in Men

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Much clinical and scientific attention has been directed to changes in the individual serum lipids in men with coronary disease, and the effects upon these determinations of various hormonal, dietary, or other regimens. However, it was shown by Peters and Mann and by Popjak many years ago that there is a fixed and constant mathematical (regression) relationship between cholesterol and the phospholipids not only in a wide variety of clinical states and ages in man, but also in a variety of animal species other than man. We have verified this fixed, mathematical relationship in normal men, men with various debilitating diseases, men recovered from myocardial infarction, and men recovered from a cerebrovascular accident, all groups being also studied according to age. The relationship of cholesterol to the per cent of β-lipoprotein was also constant, regardless of age and clinical state. The basic mechanisms, of whatever sort, that regulate the quantitative relationships among these lipids and lipoproteins therefore appear remarkably stable under the greatest variety of age and clinical states in man. In a clinical trial of placebo, ethinyl estradiol, and Premarin involving approximately 300 men recovered from myocardial infarction, subjects being randomized among the treatment groups and given doses of estrogen only sufficient to produce minimal breast changes, the foregoing interlipid relationships remained entirely unaltered in subjects treated with either placebo or Premarin. There was a considerable and statistically significant alteration in these interlipid relationships under ethinyl estradiol treatment, suggesting that one or more of the basic regulatory mechanisms may have been altered. Ethinyl estradiol, however, failed to alter the survival rate, while Premarin significantly increased survival. This emphasizes the dissociation between survival and lipid effects of estrogen therapy in men with myocardial infarction.

Assessment of an Indicator-Dilution Technic for Quantitating Aortic Regurgitation by Means of an Electromagnetic Flowmeter (P)

Hiram W. Marshall, Donald A. Malooly, David E. Donald, Egas Armelin, and Earl H. Wood, Rochester, Minnesota

The Spencer flowmeter probe was placed on the proximal portion of the ascending aorta of open-chest, anesthetized dogs. Phasic aortic flow was recorded simultaneously with dilution curves from the left ventricle and femoral artery after injections of indocyanine green of 1-second duration into the aorta 1 cm. downstream to the valve. Flowmeter calibrations by bidirectional perfusion of the aorta at necropsy were in good agreement with stroke-volume values from femoral-artery dilution curves obtained in vivo (r=0.93). After a series of determinations in the control situation, in which no immediately appearing dye was detected in the left ventricle, aortic regurgitation was created by valvotomy via a carotid artery. Metered regurgitant flows ranged from 0.1 to 3.8 L./min. The ratios of the curves of the immediately appearing portion of left ventricular dye(LV_A) to the area of the simultaneous femoral artery curve (FA_A) ranged from 0.05 to 1.03 after valvotomy and showed a good correlation (r=0.91) with the ratio of metered regurgitant flow (Q_R) to metered total forward flow (Q_F) in 102 simultaneous pairs of determinations in 6 dogs. However, there was a systematic difference between dye curve and flowmeter values such that $Q_R/Q_F = 0.82\ (LV_A/FA_A) \pm 0.12$. Calculation of regurgitant flow from the regurgitant fraction (Q_R/Q_F) obtained in this manner requires measurement of cardiac output (Q_S) and use of the equation $Q_R = Q_S\ (Q_R/Q_F) \div (1 - Q_R/Q_F)$. Because of the nature of this relationship, the error in estimation of Q_R increases with increasing values for regurgitant fraction, an overestimate of regurgitant fraction of 0.1 causing an overestimate of 14 per cent in Q_R (when Q_R is expressed as a per cent of cardiac output) for a fraction of 0.2 and of 50 per cent for a fraction of 0.5. Clinical application of these measurements deserves study.

False Paradoxic Movement of the Left Ventricle Simulating Myocardial Aneurysm

Jack M. Martt and Theodore E. Keats, Columbia, Missouri

False paradoxic movement of the posterior wall of the left ventricle if radiographed in the lateral projection at the proper moment may simulate myocardial aneurysm. This erroneous impression may be further reinforced by apparent paradoxic movement of this portion of the heart as seen fluoroscopically.

This entity has apparently not been previously described. Our interpretations in normal subjects indicates that this phenomenon represents a normal movement of this portion of the left ventricle when observed in full inspiration.

This study includes correlation of this phenomenon, as demonstrated by cineradiography, with the electrocardiogram, ballistocardiogram, arterial pressure pulse, and with contrast ventriculography,

with the purpose of identifying the location of the false paradoxic movement and its time of occurrence in the cardiac cycle. An explanation for this movement is offered.

Frequency-Intensity Analysis of Normal and Abnormal Heart Sounds

Daniel Mason, Bernard L. Segal, William Strong, and Norman B. Burke, Philadelphia, Pennsylvania

The clinical evaluation of pitch and loudness often does not correlate with the more precise electronic measurement of frequency and intensity. Consequently, errors may be made in differentiating these characteristics of normal and abnormal heart sounds. For example, a loud first sound at the cardiac apex may be confused with a sharp apical first sound of mitral stenosis.

A technic has been devised whereby precise measurement of the frequency ranges and intensities of the heart sounds are made. By means of a specially constructed barium titanate microphone, the heart sounds are recorded on magnetic tape. These recordings then are played back feeding a narrow band width filter system. At preselected frequencies, the intensity content of the recordings are evaluated. A graphic portrayal of results has been made.

From these, precise delineation of the frequency-intensity characteristics of a normal heart sound, sharp first sound of mitral stenosis, opening snap, diastolic gallop rhythms, systolic click, ringing aortic second sound, as well as other sounds, have been made. These frequency-intensity patterns appear to be more specific for the particular heart sound evaluated.

Humoral Regulation of Secretion of Renal Pressor Substances (P)

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Although blood pressure may regulate secretion of renal pressor substances, there is also some evidence of a humoral regulation. To test the relative significance of these two mechanisms, groups of rats were treated with a crude hog kidney extract containing 1 Goldblatt unit per ml. (3 U./day), a semipurified hog kidney extract containing 30 G.U. per ml. (90 U./day), metareminol (3 to 6 mg./day) or hydralazine (6 mg./day). A control group received a saline suspension of hog liver. All injections were subcutaneous, The crude kidney extract had no effect on blood pressure or proteinuria, while the partially purified extract caused a sustained rise of about 50 mm. Hg and increased proteinuria 30 times. On the fourth and fifth day of treatment, kidneys were removed for extraction and for grafting. Pressor activity in renal secretions averaged: 20.6 ± 2.9 in controls; 9.1 ± 3.1 with semipurified extract ($p= 0.02$); 2. ± 2.7 with crude extract ($p<0.01$); 18 ± 2. with metaraminol ($p= 0.2$); and 24.5 ± 2.8 hydralazine ($p=0.4$). *P* value between hydralazine and metaraminol was less than 0.1. The pressor activity contained in kidneys remained unchanged in all groups. In conclusion, significant inhibition of release of pressor substances occurred only after treatment with kidney extracts. Since the crude extract was apparently the most active in reducing secretion without any detectable effect on pressure and proteinuria, it followed either that this inhibition is caused by nonpressor doses of renin or that there is another factor which is partly lost during purification. This suggests the existence of a humoral interplay between kidneys in controlling renal pressor secretions.

Anticoagulant Therapy in the Premonitory Phase of Acute Coronary Occlusion ("Impending Infarction")

Arthur M. Master, New York, New York

Eighty patients not receiving anticoagulant preparations were compared with 55 who were either already on these drugs or received them immediately at the onset of the impending infarction. These were administered before any evidence of pathologic changes occurred in the heart by clinical, electrocardiographic, and laboratory observation.

The patients were sufferers from angina pectoris but abruptly developed changes in the characteristics of the pain. The pain now occurred with increasing frequency, severity, and duration on less or even no effort. The quality, location, radiation, and response to nitroglycerin were altered. Patients who sustained one or more isolated episodes of severe chest pain were not included, since infarction may have already commenced.

In conclusion, no acute coronary episode occurred in 61 of the 80 control patients; 14 developed acute coronary insufficiency without occlusion; 3 suffered acute coronary occlusion (2 of whom died) and 2 developed status anginosus.

In the 55 patients who were given anticoagulant drugs, no acute coronary episode appeared in 23, acute coronary insufficiency resulted in 20, acute coronary occlusion in 12. Six died, 1 of whom had developed status anginosus.

Those receiving anticoagulant drugs in this type of impending infarction did not fare as well as the "controls." Hence, anticoagulant therapy may be contraindicated in "impending" infarction.

This report does not reflect on the use of anticoagulant drugs after an acute coronary occlusion,

nor on long-term therapy in coronary diseases, but is solely concerned with "impending infarction" as we have defined it.

Elevated Blood Pressure in Individuals from 20 to 100 Years of Age

Arthur M. Master, Richard P. Lasser, and Ephraim Donoso, New York, New York

The purpose of this investigation is to establish a line of demarcation best to separate blood-pressure levels compatible with average life expectancy, from those which generally presage the development of cardiovascular and renal impairment and shortened life span.

Life insurance companies have published extensive tables relating systolic and diastolic blood pressure to mortality rate in subjects 20 to 69 years of age. Our average blood-pressure readings on previously published "apparently healthy" people corresponded with those of the "good risks" of the insurance study. The upper limits of our standard deviation from the mean corresponded to relative mortality ratio of 160 to 200 per cent and the upper limit of our +2 standard-deviation readings carried mortality rates of 250 to 300 per cent. From these data we constructed tables, by sex, and 5-year age groups, indicating readings that we consider "normal," "borderline," and definitely "hypertensive."

For those 69 years and older, an "apparently healthy" group (2,925 men, 2,694 women) was compared with 1,189 men and women of the same age who suffered from authenticated hypertensive cardiovascular disease. Comparisons of "average" values, modes, standard deviations, and "discriminant function analysis" were made between these 2 groups. We have come to the tentative conclusion that blood pressures above 175/95 in men and 185/95 in women, are abnormal at 65 years and over and are likely to be associated with involvement of the heart, blood vessels, brain, or kidneys.

QX/QT and QT Ratios in the Diagnosis of Ischemic Heart Disease

Arthur M. Master and Isadore Rosenfeld, New York, New York

Postexercise (Master test) electrocardiograms were analyzed in 596 consecutive patients because of chest pain. All resting tracings were perfectly normal. In 292 cases, the "2-step" was negative. In the remaining 304 patients, attention was focused on the RS-T segment depression, i.e., (a) whether "ischemic" or "j" type, (b) duration of depression in each cardiac cycle (QX/QT ratio), and (c) changes in the QT-interval.

Ischemic RS-T depressions (108 cases) were almost diagnostic of ischemic heart disease, yielding only 4.5 per cent "false positives."

"J" or junctional depression (196 cases), although thought to be functional by many, occurred in 30 per cent of patients with myocardial ischemia. These ambiguous "j" responses were greatly clarified by application of the QX/QT ratio, namely, the duration of RS-T depression (QX) as a percentile of electrical systole (QT). QX/QT ratios greater than 50 per cent were found in 55 of 62 organic cases; values less than 50 per cent, in 131 of 134 functional cases. These results were further refined by QT-ratio measurement.

Prolongation of the QT interval is observed in myocardial ischemia. Regardless of whether or not RS-T depressions occurred, and independent of configuration, the QT ratio was prolonged beyond 1.08 after exercise in 177 of 180 cases with heart disease. Values below 1.08 were observed in 408 of the remaining 416 functional cases.

Vectorcardiographic Diagnosis of Peri-infarction Block (Frank System)

Joan W. Mayer, Louis Lemberg, and Agustin Castellanos, Jr., Miami, Florida

The term "peri-infarction block" has been used to describe that form of intraventricular block produced by anomalous spread of conduction through muscle located at the periphery of electrically inert tissue. Various electrocardiographic criteria have been cited in the literature. As a result of our studies the following points have been developed: the criteria for vectorcardiographic diagnosis determined; the abnormal electrophysiologic changes are more clearly seen in the vectorcardiogram; electrocardiographic criteria are extended to include cases with normal QRS duration.

A vectorcardiographic study of over 50 patients with known myocardial infarctions and electrocardiographic evidence of conduction disturbance other than right bundle-branch block or left bundle-branch block was made. Using these cases vectorcardiographic criteria for the diagnosis of peri-infarction block in a single recording were established. The focal point of the vectorcardiographic diagnosis rests on the direction and terminal delay of the vector loop. These changes are to be differentiated from left bundle-branch block when the delay is predominantly medial and from right bundle-branch block when the delayed terminal or preterminal appendage does not form a 180 degree angle with the initial vector.

The criteria for diagnosis are the following: (1) initial QRS changes characteristic of myocardial infarction, (2) initial forces opposed in direction to the terminal vectors, (3) terminal

delay greater than 30 msec., and (4) normal or prolonged QRS duration.

In all cases the direction of the terminal forces was dependent on the location of the initial ones suggesting that both the initial and terminal delay in intraventricular conduction is due to the same lesion.

Forgotten Factor in Cardiac Output Measurements

John E. Mazuzan, Jr., Calvin Hanna, and John Abajian, Jr., Burlington, Vermont

The changing functional capabilities of the heart under the influence of various anesthetic agents is of special interest to the anesthesiologist. Recently the development of a new indicator dye (Coomasie blue) and a reliable earpiece densitometer has permitted *serial* measurements of cardiac output in a large segment of the surgical population before induction, postinduction, during surgery, and on emergence.

Single agents with oxygen as a carrier gas and minimal narcotic with antagonist and scopolamine premedication were used. Measurements of cardiac output, pulse rate, and blood pressure were made on 14 surgical patients after 10 minutes of air breathing via an anesthesia machine and after 15 minutes of 100 per cent oxygen breathing. Cardiac output was lowered with oxygen breathing (average reduction of 34 per cent) in all patients; pulse rate fell in 80 per cent of the group.

Considerable emphasis has been placed on the importance of considering premedication influence when evaluating output studies concerning anesthetic effects. Six patients were studied with either barbiturate premedication or with no medication; there were no significant changes in the results. Since most anesthetic technics incorporate high oxygen concentrations, a considerable portion of the output fall previously attributed to the anesthetic is a reflection of physiologic adjustment secondary to increased availability of oxygen for extraction per unit volume of blood (Fick principle). Comparison of the cardiac output under anesthesia against oxygen controls will better reflect the influence of the anesthetic than comparisons with the usually employed air controls. This factor appears more significant than the often-mentioned premedication effects.

An Approach to the Prevention of Initial Attacks of Rheumatic Fever: II. Second Field Trial

John A. Mazzarella, James M. Jablon, and Milton S. Saslaw, Miami, Florida

This program was designed to test the feasibility of prevention of initial attacks of rheumatic fever. It incorporated the fluorescent-antibody technic for rapid determination of group A β-hemolytic streptococci in the throat to permit prompt treatment of such infections when clinical illness was present.

Eight elementary schools representing white populations of high, middle, and low income, and Negro schools (2 each) were selected from the schools of Dade County, Florida by random sampling. Three hundred eighty-eight students randomly selected were under surveillance.

Prompt reporting and screening of absentees was carried out daily. Students absent because of respiratory illness or fever of unknown origin were visited by a public health nurse, who recorded illness data and took throat swabs. Fluorescent and cultural technics were employed on each specimen. If fluorescent positive, the family physician was notified the same day and informed of the recommended therapy of the American Heart Association.

Two hundred thirty-seven specimens have been studied. Eighteen samples were identified by fluorescence as group A organisms; 13 were verified by culture. Of the 18 children involved, 14 received therapy, while 4 remained untreated.

This study has shown the feasibility of the prevention of initial attacks of rheumatic fever in view of the rapid identification of group A organisms made possible by the fluorescent-antibody technic. It justifies and warrants further research to determine its applicability to larger population groups. Testing such a program should be conducted in areas with varying incidence rates of rheumatic fever.

Usefulness of Vectorcardiography in the Diagnosis of "Atypical" Myocardial Infarctions: I. True Posterior Myocardial Infarction (P)

Donald McCaughan and Conger Williams, Boston, Massachusetts

True posterior myocardial infarction occurs as an isolated phenomenon or as a more widespread process, involving contiguous parts of the inferior or lateral myocardial walls. Theoretically, it should be possible, using currently acceptable criteria, to make a diagnosis in all cases with the standard electrocardiogram.

To test the validity of this concept, 39 cases that had been diagnosed as posterior infarction were assembled from our collection of Frank vectorcardiograms. The standard electrocardiograms, taken at the same time, were reviewed. Twenty-nine of these cases had convincing evidence of myocardial infarction (history, physical examination, other laboratory tests). Two of this group came to autopsy. Ten had classical symptoms of

coronary insufficiency but no evidence of infarction other than the vectorcardoigram.

The vectorcardiogram in all cases showed the following: (1) anterior deviation of the horizontal plane half-area vector, so that more than 40 per cent of the QRS area lay in front of the E point; (2) prolongation of the anterior forces to at least 0.04 second; (3) T vector directed more anteriorly than normally. In addition, 20 cases showed abnormal orientation of the initial forces to the right or superiorly, evident also in the electrocardiogram. The remaining 19 cases showed only isolated posterior wall involvement, and of these only 4 had an R wave greater than the S in V_1. Fourteen had high T waves over the right precordium.

Our experience suggests that the Frank vectorcardiogram may be more useful in establishing the diagnosis of posterior myocardial infarction than is the standard electrocardiogram.

Observations on Serum-Cholesterol Levels in the Twin Population of Evans County, Georgia (P)

John R. McDonough, Curtis G. Hames, Claxton, Georgia, B. G. Greenberg, Chapel Hill, North Carolina, Louis H. Griffin, Jr., and Andrew J. Edwards, Jr., Claxton, Georgia

Fifty-six pairs of twins ranging in age from 5 to 63 years were identified by means of a complete household census of Evans County, Georgia. Blood for typing and serum cholesterol was obtained on all 112 individuals by household visits. Twin pairs were differenciated into monozygotic or dizygotic by physical similarity, blood type, and serum haptoglobins.

Each serum was analyzed for cholesterol in duplicate using a modification of the Abell method. Cholesterol levels ranged from 104 to 233 mg. per 100 cc. at age 5 to 14 years; 83 to 225 mg. per 100 cc. at age 15 to 29 years; and 122 to 271 mg. per 100 cc. at age 30 to 63 years. The mean intrapair difference in serum cholesterol, expressed as mg. per 100 cc. was 13.9 for 24 pairs of monozygotic twins and 30.5 for 32 pairs of dizygotic twins. The difference between these means was highly significant ($p < 0.01$). Monozygotic twins had a significantly lower mean intrapair difference for each of the 3 age-groups; but the difference was striking and highly significant ($p < 0.01$) at age 5 to 14 years with a mean intrapair difference of 7.5 for monozygotic twins and 22.6 for dizygotic twins. This intrapair difference for monozygotic twins aged 5 to 14 years exceeded but did not differ significantly from measurement error.

These data suggest that, despite great variation in cholesterol level between persons at all ages, the levels observed during youth may be quite precisely predetermined by genetic mechanisms. Further study is being made to determine if these intrapair differences are a result of variations in age, race, or sex.

Angina Pectoris with Coexisting Skeletal Chest Pain

James B. McElroy, Birmingham, Alabama

It is well known that certain painful skeletal conditions, such as the shoulder-hand syndrome, may follow myocardial infarction. However, it is not generally appreciated that people with angina pectoris, without myocardial infarction, have a high incidence of anterior chest pain of skeletal origin.

The records of 2,213 referred medical patients were reviewed. Three hundred and five patients presented convincing evidence of angina pectoris. Three hundred and five control subjects were selected by the absence of any cardiac disorder and were paired as to age, decade, and sex with the angina group. The incidence of anterior chest-wall pain of skeletal origin was determined for both groups.

Clinical evidence of anterior skeletal chest pain was present in 51 per cent of patients with angina pectoris and 23.1 per cent of controls. This represents a significant difference ($p < 0.001$).

In a considerable fraction of the patients with angina, the more important ischemic pain was confused or even masked by the coexistence of the innocent disorder.

These findings demonstrate that (at least in this series of patients) anterior skeletal chest pain is more common in people with angina pectoris than in individuals of the same age, decade, and sex with healthy hearts. The mechanism of skeletal chest pain associated with coronary-artery disease is unknown. It is, therefore, important to institute a meticulous search for coronary-artery disease in any patient presenting with obvious chest-wall pain.

Pulmonary Hypertensive Effects of Bretylium Tosylate (P)

Charles J. McGaff and Leonard Leight, Louisville, Kentucky

Hemodynamics were measured 6 to 70 minutes after intravenous injection of bretylium tosylate (20 to 150 mg./Kg.) in 10 closed-chest anesthetized dogs with respiration maintained by positive pressure. Cardiac output (CO) and pulmonary blood volume (PBV) were measured by indicator dilution. Mean pressures were recorded in the pulmonary artery (PA), left atrium (LA), femoral

artery (FA), trachea (T), and pulmonary capillary wedge (PC).

Pulmonary vascular resistance (PVR) and PA pressure rose significantly in all, means equaling +430 dynes sec. cm.$^{-5}$/10 Kg. and +8 mm. Hg, respectively ($p < 0.005$). Systemic vascular resistance, CO, PBV, LA, PC, T, and heart rate did not change significantly. Arterial oxygen saturation fell in 3 of 5 measurements. Infusions of acetylcholine or phentolamine had no effect on the elevated PVR caused by bretylium.

Bretylium tosylate elevates PVR in man, sheep, and, by this study, the dog. The change is at arteriolar level, since PA rises while other pressures do not. Elevated viscosity owing to mildly increased hematocrit does not account for the total elevation in PVR. The cause of this increased hematocrit is obscure.

Bretylium is less active on pulmonary vessels than serotonin, since a decrease in PBV does not accompany an increase in PVR as it does with serotonin. Constriction of pulmonary vessels by bretylium is probably limited to small arterioles, since PVR changed without a shift in PBV.

Behavior of Renal and Femoral Vascular Resistances after Hypertensive Stimuli (P)

John C. McGiff, Philadelphia, Pennsylvania

Simultaneous and continuous observations of renal and femoral blood flows of the anesthetized dog during application of hypertensive stimuli permit delineation of the sensitivity of these regional beds to various humoral and nervous stimuli. To intravenously administered levarterenol and angiotensin, renal resistance was increased more than femoral resistance. To increased intracranial pressure, the regional resistances were comparably elevated, unless the control blood pressure and flows were low. In the latter case femoral resistance may fall, whereas renal resistance always increases. Baroreceptor activity and chemoreceptor activity elicited a greater increase in femoral resistance than renal resistance.

In an attempt to abolish sympathetic vasoconstrictor activity, guanethidine and bretylium were employed during the stimulus of increased intracranial pressure. The pressor response and reduction of limb and renal blood flows after increased intracranial pressure were reversed or lessened after employment of these agents. Femoral and renal resistances are reduced to or toward control with the continued application of increased intracranial pressure after administration of either guanethidine or bretylium. Femoral resistance is reduced more than renal resistance. This latter difference in regional resistances is presumably due to the greater sensitivity of the renal vasculature to catecholamines, the activity of which is unopposed by bretylium or guanethidine. The administration of these agents in the resting anesthetized dog produces a greater reduction in femoral than renal resistances. This last effect is related to the greater degree of sympathetic tone involving the vessels of skeletal muscle than of those of the kidney.

Total Prosthetic Reconstruction of the Aortic Valve: Clinical Experience (P)

Dwight C. McGoon, Rochester, Minnesota

In 20 patients the diseased aortic valve has been totally reconstructed by means of a prosthesis. The primary indication for use of the prosthesis was the presence of an incompetent valve, which was judged not amenable to other methods of repair. Replacement of a calcified stenotic valve was required in 5 of these patients. Function of all but 2 of the reconstructed valves proved satisfactory. Ten patients lived to be dismissed from the hospital, and to date no late failures or deaths are known. The morbidity and mortality associated with the procedure have been related primarily to the technical problems attending extensive surgery in a group of patients suffering from advanced cardiac disease.

The unique feature of the scheme of this prosthesis is that it adds length to the usable and functional components of the natural valve, and does not require bold excision of these parts. The prosthesis is made of fine teflon thread knitted into a tube of cloth, and is trimmed at the time of surgery to the requirements of the individual valve. Insertion of the prosthesis is rather readily accomplished, and evidence to date suggests durability of the repair. A 1-minute movie showing function of the prosthesis in the hearts of nonsurviving patients and in animal hearts has been made.

At this time, the accumulated experience with this technic suggests it to be worthy of continued clinical and experimental trial.

Postpericardiotomy Syndrome: Its Relationship to Ambulation in the Presence of "Benign" Pericardial or Pleural Reaction (P)

John B. McGuinness and Helen B. Taussig, Baltimore, Maryland

The postpericardiotomy syndrome is defined as a delayed pericardial or pleural reaction after opening of the pericardium. The syndrome is characterized by fever, chest pain, and signs of pericardial and sometimes pleural inflammation;

as is well known, the condition tends to recur.

The cases fulfilling these criteria in children operated on for congenital cardiac defect within the past 5 years in the Johns Hopkins Hospital have been reviewed. On the basis of the observation that several patients who were discharged with evidence of a benign pericardial friction rub or pleural reaction subsequently developed a postpericardiotomy syndrome, special attention has been paid to the presence or absence of pericardial or pleural friction rub, pyrexia, and evidence of pleural or pericardial reaction on x-ray at the time of ambulation.

Examples of patients with an apparently benign course who developed the postpericardiotomy syndrome will be contrasted with patients in whom a pleural or pericardial reaction persisted but in whom the full syndrome appears to have been averted by slow ambulation.

These observations suggest that the postpericardiotomy syndrome is related to ambulation in the presence of persistent pleural or pericardial inflammation and may be prevented by conservative treatment, namely, rest in bed, until all signs of pleural and pericardial activity have completely subsided.

Segmental Coronary Vascular Resistance

William P. McKeever, Hildegarde V. Braun, Joseph D. Croft, Jr., and Donald M. Coder, Evanston, Illinois

Previous studies of coronary vascular resistance have been concerned with overall resistance. To elucidate the role of the different types of vessel in the coronary tree and determine the contribution of interarterial anastomoses, the following studies were performed.

Mongrel dogs were used. The left coronary was cannulated and perfused at a constant rate from a donor animal. The heart was excised from the chest and placed on a special receptacle. Polyethylene catheters (I.D., 0.5 mm.) were introduced into a small coronary artery and vein and passed distally and proximally respectively until wedged. Pressures were monitored from both catheters and the main coronary artery. Since flow was constant, resistance changes could be measured as pressure drops from main coronary artery to small artery (arterial segment), from small artery to small vein (small-vessel segment), and from small vein to atmosphere (venous segment).

An average pressure drop of 34.5 mm. Hg (20 experiments) occurs in the arterial segment. A lesser drop of 14.4 mm. Hg occurs in the small-vessel segment. This suggests that the small coronary arteries of the dog are functional end arteries with no functioning interarterial anastomoses. That resistance to flow varies independently of extravascular control and that different segments of the bed may function independently of one another is demonstrated by infusion of vasoactive substances. Potassium in low concentration initially dilates all segments and subsequently constricts arterial and small-vessel segments. Serotonin dilates arterial and small-vessel segments and in most instances constricts the venous bed.

Buerger Syndrome in the Orient and in the United States

Victor A. McKusick and Willard S. Harris, Baltimore, Maryland

Twenty-eight Korean males with "Buerger's disease" and an unaffected comparison group were studied at Presbyterian Medical Center, Chonju, Korea.

Onset occurred before 35 years in 20. Involvement of both upper and lower extremities occurred in 17, 4-extremity involvement in 11. No evidence of visceral vascular disease was discovered. Serum cholesterols were 196.8 mg. per cent (S.D. 20.3) and 201.3 (S.D. 27.2) in study and comparison groups respectively; fasting blood sugars 93.1 mg. per cent (S.D. 9.1) and 91.3 (S.D. 5.3).

Arteriograms and aortograms revealed, in most, occlusive arterial disease in the forearm and in the midthigh area or lower.

Twenty-three were farmers, a larger proportion than expected. Twenty-seven were of the lowest socioeconomic status. No dairy products or eggs were eaten, meat rarely, fish rather rarely. All were cigarette smokers. Exposure and trauma were excessive.

Most of the cases satisfy criteria for the diagnosis of the Buerger syndrome—occlusive vascular disease in young male smokers, often involving arms as well as legs, without diabetes, hypercholesterolemia, or disease of heart and aorta. Atherosclerosis and embolism were excluded in most. Recent autopsies reveal a low prevalence of atherosclerosis in Koreans. Visits to 6 medical centers in Japan revealed an appreciable frequency of cases of the Buerger syndrome and a relative rarity of atherosclerotic and thromboembolic disease.

At Johns Hopkins Hospital 25 cases of Buerger syndrome were studied. A primary angiitis could not be established in many. One patient with 3-extremity involvement developed an epididymal mass from angiitis of the spermatic vessels.

Shock after Excision of Pheochromocytoma: Mechanism and Clinical and Laboratory Data

Jasper L. McPhail and James D. Hardy, Jackson, Mississippi

After excision of a functioning pheochromocytoma, the majority of patients exhibit significant hypotension, often profound, for variable periods. The hypotheses advanced to explain the mechanism of this shock have centered around (a) left heart failure and (b) peripherovascular collapse. In recent years the peripherovascular theory, with an implied lack of arteriolar tonus rendering the vascular bed disproportionately large relative to the available blood volume, has enjoyed increased popularity. The present studies add additional support to the peripherovascular hypothesis.

Profound shock, in which the blood pressure for 48 hours was unobtainable without norepinephrine infusion, followed excision of a pheochromocytoma in a patient studied carefully before, during, and after operation (E and NE levels in peripheral plasma, urine, and venous drainage of tumor during surgery). Massive dosage of NE I.V. was mandatory.

In 10 dogs NE was infused I.V. to maintain systolic blood pressure above 200 mm. Hg. Four died of pulmonary edema or ventricular fibrillation. Six dogs survived 4 hours of infusion. Two of these died in shock after cessation of the NE; the other 4 exhibited severe temporary hypotention, followed by a brief period of hypertension and then normotension. Plasma NE levels available were measured. Ten additional dogs are being studied.

The data support the view that shock after excision of pheochromocytoma is due primarily to a relatively plegic state of the peripheral vascular bed. This has a bearing upon clinical NE therapy in other shock states, where the need for increasing amounts of NE to maintain blood pressure may at times reflect a decreasing capacity of the peripheral vessels to accept the chemical stimulus of NE rather than progressive deterioration of the overall condition of the patient.

Prognosis of Thromboangiitis Obliterans and Arteriosclerosis Obliterans

James R. McPherson, John L. Juergens, and Ray W. Gifford, Jr., Rochester, Minnesota

The records of 268 patients, age 45 years or less when the diagnosis of chronic occlusive arterial disease was first made during the 5-year period 1945 through 1949, were reviewed. Clinical criteria for categorizing the cases as thromboangiitis obliterans rather than as arteriosclerosis obliterans included: ischemia of upper as well as lower extremity, history of superficial thrombophlebitis, and the absence of arterial calcification, hypercholesteremia, and heart disease that could have been responsible for arterial emboli. Forty-five patients who were considered to have thromboangiitis obliterans comprised group 1; 104 who probably had thromboangiitis obliterans, group 2; 78 who had arteriosclerosis obliterans, group 3; and 41 who probably had arteriosclerosis obliterans, group 4. At or before the time of diagnosis, major or minor amputations were necessary for 29 per cent of patients in group 1, 20 per cent in group 2, 1 per cent in group 3, and 10 per cent in group 4.

Follow-up information was obtained in 75 per cent of cases. The incidence of subsequent amputations in the respective groups was 19 per cent, 8 per cent, 3 per cent, and 10 per cent. The 5- and 10-year survival rates for the patients were: group 1, 100 and 85.7 per cent; group 2, 93.3 and 88.4 per cent; group 3, 75 and 64.5 per cent; group 4, 76.5 and 70.5 per cent respectively. These significant differences with respect to survival of life and limb suggest that thromboangiitis obliterans is a clinical entity and a useful diagnostic category that should not be discarded.

Isolated Anomalous Connection of a Great Vein to the Left Atrium

W. R. Meadows, Hines, Illinois, Ingemar Bergstrand, Lund, Sweden, and John T. Sharp, Hines, Illinois

A 37-year-old Negro male was referred to the cardiopulmonary laboratory for evaluation of cyanosis (oxygen saturation 82 per cent), clubbing and erythrocytosis. Although hospitalized 6 years for far-advanced pulmonary tuberculosis, he had otherwise been unrestricted in his occupation as a laborer. Except for a prolonged P-R interval and changes on electrocardiogram attributed to left atrial and left ventricular hypertrophy, there were no clinical or radiologic findings to suggest the presence of heart disease.

Cardiac catheterization from a median basilic vein and a saphenous vein with oximetry and venous angiography established the diagnosis of isolated anomalous connection of the inferior vena cava to the left atrium. Dye-dilution curves recorded at a radial artery after venous injections of indocyanine green showed unique features including a distinctly shortened circulation time from the femoral vein as compared to that from an antecubital vein.

The literature contains 1 case of isolated anomalous connection of the inferior vena cava to the left atrium and 2 in which the superior vena cava drained only into the left atrium. The data permit the definition of a syndrome: central cyanosis, normal heart on x-ray and physical examination, and left ventricular hypertrophy on electrocardiogram. Indicator-dilution curves after venous injection of dye will confirm the diagnosis.

Congenital Malformations of the Heart Associated with Congenital Anomaly of the Urinary Tract

Ali Mehrizi and Helen B. Taussig, Baltimore, Maryland

A review of 2,600 autopsy reports of the Johns Hopkins Hospital revealed 279 cases in which there were major anomalies of the urinary tract, such as horse-shoe kidney, absence or hypoplasia of one kidney, polycystic kidney, or malformed or displaced kidneys, etc. Sixty-six (24 per cent) of these cases were found to have associated cardiac malformations. In 29 cases, there was an isolated ventricular septal defect: in 13 of these patients, death occurred in the first week of life and in 10 additional, within the first year. Three of the remaining 6 died of congestive heart failure and 3 died at operation for correction of the ventricular septal defect. All 6 showed microscopic evidence of severe pulmonary vascular lesions.

Because of the high incidence of ventricular septal defect associated with major urinary-tract anomalies, the autopsy cases between 1927 and 1960 were reviewed to determine the incidence of anomaly of the urinary tract in patients with ventricular septal defect. Eighty-seven cases of ventricular septal defect were found. Twenty-two (24 per cent) also had major malformations of the urinary tract. Fourteen showed vascular changes in the lungs: 6 of these 14 were in the above group of urinary-tract anomalies; the other 8 cases in which pulmonary vascular changes were found were not associated with urinary-tract anomalies.

In summary, the review reveals a relatively high incidence of the association of ventricular septal defect and major urinary-tract abnormalities, but the relation of such abnormalities to pulmonary vascular lesions remains obscure.

Clinical, Hemodynamic, and Pathologic Diagnosis of Muscular Subvalvular Aortic Stenosis

Hermann Menges, Jr., Robert O. Brandenburg, and Arnold L. Brown, Jr., Rochester, Minnesota

Eight anatomically proved cases of muscular obstruction to left ventricular outflow have been studied. Three were examined at necropsy, and 5 were identified at surgery. The most common symptoms were angina, dyspnea, and palpitations, although congestive heart failure occurred and 1 patient died suddenly. A systolic murmur along the left sternal border was the most consistent physical finding, but a normal aortic second sound, the presence of third and fourth heart sounds, splitting of the second sound, and absence of a diastolic murmur were other helpful clinical guides. Withdrawal pressures from the left ventricle revealed a characteristic infundibular pressure zone. Other hemodynamic findings included: an anacrotic notch on the left ventricular pressure tracing, a rapidly ascending bisferious central pulse, and a small compensatory beat after extrasystole. At surgery and at necropsy, cardiomegaly with disproportionate thickening of the interventricular septum was noted. The average thickness of the left ventricle and the width of the upper muscular septum were measured in the necropsy specimens and a ratio established between the 2. A control group of 20 normal and 50 hypertrophied hearts was similarly evaluated. In all cases of muscular subvalvular stenosis the septal-ventricular ratio exceeded 1.5, whereas in the control group it was (with 1 exception) less than 1.25. These measurements indicate that the relative width of the septum and left ventricle is significant in establishing the diagnosis of muscular obstruction to left ventricular outflow at the time of necropsy. Microscopic alterations were minimal.

Correlation of Coronary Anatomy and Physiology in Man

Joseph V. Messer, Arthur A. Sasahara, David Littmann, and Richard Gorlin, Boston, Massachusetts

The relationship between human coronary anatomy, physiology, and symptomatology is of major importance in evaluating the normal and diseased coronary circulation. Preliminary observations have been made in a comparative study utilizing: (1) independent clinical evaluation of anginal history (AP), physical findings, and rest-exercise electrocardiogram (ETT); (2) coronary arteriography (CA) for detection of major vessel unfilling, localized obstruction, spotty vessel opacification, tortuosity, branching, localized dilatation, and apparent recanalization; and (3) measurement of coronary functional reserve (CFR) by coronary venous catheterization studies of blood flow and oxygen-supply patterns during rest and exercise. Inadequate CFR was judged by an exercise fall in absolute coronary venous oxygen saturation of more than 5 per cent and increase of myocardial oxygen extraction coefficient of more than 3 per cent over resting values. Excellent correlation among the presence or absence of anginal pain and the results of exercise tolerance tests, coronary arteriography, and evaluation of coronary functional reserve occurred in 5 of 7 subjects studied thus far. The sixth subject with abnormal coronary functional reserve, coronary arteriography, and diffuse obliterative coronary disease at subsequent necropsy had a normal ETT. The seventh anginal subject had no detectable abnormality of CFR despite abnormality in arteriography and exercise tolerance test. Such correlative studies should pro-

vide improved anatomic classification of coronary disease and its resulting functional significance. Hopefully, this should indicate the most sensitive and important tests to be used in assessing the coronary circulation.

Studies Concerning the Mechanism of the Hypersensitivity Reaction of the Heart (P)

George F. Mikulicich, Alhambra, California, and Y. T. Oester, Chicago, Illinois

This report summarizes the findings resulting from the experimentally induced hypersensitivity heart reaction in animals, primarily in rabbits. The problem was studied from several different points of experimental approach.

I. The course of the heart reaction was recorded by electrocardiograph, after the intravenous antigen injection (horse serum and egg-white albumin), 18 days after sensitization. The typical changes usually last 3 to 15 minutes beginning 1½ to 2 minutes after the injection of antigen. These typical changes are a prolongation of the P-R interval, up to A-V block; ventricular extrasystoles, with occasional short periods of ventricular fibrillation; elevation and prolongation of the QRS complex, often similar to bundle-branch block; and finally ST changes, similar to the pattern seen in ischemia and infarction.

II. The pathologic tissue changes, principally inflammation, in the heart and in the vessels of the heart and lung were determined 2 weeks after the second antigen injection.

III. The influence of the autonomic nervous system upon the course of the anaphylactic heart reaction was studied by means of experimental bilateral vagotomy and sympathectomy.

IV. The similarity of the anaphylactic heart reaction to the effect of intravenous injections of proteolytic enzymes (trypsin, fibrinolysin, streptokynase) was found. In addition, such reactions were compared to the heart reaction after intravenous histamine, and with the reactions elicited by histamine releasers (48/80, octylamine).

The possible activation of proteolytic enzymes by the antigen-antibody reaction and the probable formation of polypeptides responsible for the development of the inflammatory lesion, have been postulated. A scheme, representing the possible course and interrelationships of these reactions, summarizes these concepts.

Ventricular Endocardial Pathology Produced by Chronic Impairment of Cardiac Lymph Flow in the Dog

Albert J. Miller, Ruth Pick, and Louis N. Katz, Chicago, Illinois*

A substantial amount of information has been collected on the effects of chronic impairment of cardiac lymph flow in the dog. The observations presented at this time relate primarily to the gross and histologic changes in the ventricles.

The whole extrapericardial surgical technic of producing chronic impairment to cardiac lymph flow in the dog was similar to that previously reported. Gross pathology in dogs with significant chronic impairment of cardiac lymph flow consisted primarily of whitening, opacification, and thickening of the ventricular endocardium. These changes were most marked in the left ventricle. Dilatation of the right ventricle was found fairly often and was considered to be most likely preterminal in origin. Dilatation of the left ventricle was not encountered. Left ventricular hypertrophy was occasionally seen.

Microscopic pathology included increased endocardial elastic tissue (which, in some instances, dipped into the myocardium between the muscle bundles) and overall thickening of the endocardium. As with the gross pathology, the changes were most prominent in the left ventricle.

These studies clearly indicate that chronic impairment to cardiac lymph flow results in significant endocardial pathology, which is most characteristically found in the left ventricle. It is becoming increasingly evident that similar pathologic mechanisms may operate in man to produce endocardial elastosis. Our evidence militates against the theory that endocardial elastosis is secondary to chamber dilatation. Our findings in dogs suggest the need for pathologic re-evaluation of diseases of man characterized by ventricular endocardial elastosis, whether of known cause or idiopathic.

Epidemiologic Findings from a Community Streptococcal Control Program in Brookline, Massachusetts (P)

Joseph M. Miller, Boston, Massachusetts, Maurice M. Osborne, Palo Alto, California, Elaine K. Donnellan, and Leon J. Taubenhaus, Brookline, Massachusetts

This study has attempted to measure streptococcal-disease incidence, patterns of transmission, and frequency of complications in an open civilian population. Twenty-two private practitioners, using a simple and reliable throat-culture kit made available through the program, served as the case-finding team for primary streptococcal infections. Secondary cultures from family contacts and subsequent follow-up search for nephritis and rheumatic fever were performed by the physician or by public health personnel. All positive cultures were grouped and typed serologically.

During the first year of the program's operation (1960), a total of 663 primary cultures were processed, of which 177 (27 per cent) were posi-

tive for group A streptococci. Secondary cultures were obtained from 678 family contacts of these primary cases, and the 37 group A isolations yielded a secondary attack rate of 5.5 per cent. There was a striking and statistically significant preponderance of streptococcal illness in individuals with intact tonsils. The physician's clinical estimate of ultimate streptococcal recovery from the pharynx was inaccurate in approximately one-third of the illnesses. Penicillin-treatment failure and evidence of microscopic hematuria was also observed in this survey and is currently under further investigation. No instance of rheumatic fever occurred after penicillin treatment of streptococcal infection.

This experience has demonstrated the cooperative integration of a practical and service-oriented public health control program with private practice. Continued observations, especially during epidemic conditions, will provide a more rational basis for instituting or withholding "family prophylaxis" against streptococcal disease.

Detection of Heart Disease in Children: Results of a Mass Field Trial Using Tape-Recorded Heart Sounds (P)

Robert A. Miller, Jaques Smith, Jeremiah Stamler, Betty Hahneman, Irving Abrams, Gerald Hait, Joel Edelman, Joel Willard, and William Stevens, Chicago, Illinois

A method using tape-recorded heart sounds for detection of heart disease in school children was used in a mass field trial in 1960. Based on the 1950 census, a random stratified sample of the school population was selected, accurately reflecting the racial, socioeconomic, and environmental composition of the Chicago grammar-school population. From the tape-recorded heart sounds of this group of 33,026 children the cardiologist-listeners recalled 506 (1.5 per cent) for physical examination. Of these, 492 (97.2 per cent) children were examined, and 85 (17.2 per cent) were referred for more complete cardiac study. Of these, 14 were shown to have normal hearts. Of the 71 children with heart disease, 47 had congenital and 17 had rheumatic heart disease. The specific diagnosis was not complete in 5 children with heart disease. Two children with cardiac enlargement and disability associated with sickle-cell anemia were included.

To test the validity of the method, 34 children with known heart disease were recorded at random in a group of 3,000 students, without the knowledge of the participating cardiologists. Thirty-one of 34 (91 per cent) were detected by the tape-recording method. Two patients with aortic-insufficiency murmurs (Grade II, high pitched) were not found by the listeners. In the third case there was faulty placement of the microphone during apical recording. The murmur was not present on the tape. Finally, a study of the "nonrespondents," those children failing to participate in the program, was completed. The prevalence of heart disease in this group was much higher than in the children who did participate. It is concluded that a method that allows a few trained cardiologists to reduce the number of children requiring direct auscultation by over 98 per cent, and that finds heart disease in 1 of every 7 children recalled with a validity of approximately 91 per cent, has merit. The 2.2/1000 prevalence rate in this study is discussed in regard to 4 special schools for cardiac children in Chicago, excluded from the recorded sample, and in regard to the high incidence of heart disease in the "nonrespondent" group.

Transmission of Murmurs due to Congenital Cardiovascular Lesions

Abdol N. Moghadam, John D. Wallace, Howard F. Warner, Jerome A. Hubsher, George W. Deitz, and David H. Lewis, Philadelphia, Pennsylvania

During cardiac catheterization in patients with congenital cardiovascular lesions simultaneous recordings were made of intracardiac acoustics (catheter microphone) and chest-wall acoustics. Tape recordings were made and from these a frequency analysis was done using the Kay Cardialyzer. Results indicate that the characteristics of the murmur are set by the dynamics of the lesion. The distribution of intensity and frequency inside the heart and on the chest wall is dependent upon the orientation of the flow from which the murmur originates. The maximum frequency transmitted is limited in part by the intervening tissues. Several examples may be cited.

In patent ductus arteriosus, the time-course of the continuous murmur on the chest resembles that in the heart. The maximum frequency in systole is the same inside and out. In diastole, as intensity and frequency decrease, the decline in frequency outside is greater than that inside. With pulmonary hypertension the decreased intensity of the diastolic component and the difference in frequency transmission may make this part of the murmur inaudible on the chest. In ventricular septal defect the maximum frequency on the chest resembles that in the heart. Its localization on the chest appears dependent on the orientation of the jet as noted from the distribution of high frequency components in the right ventricle and pulmonary artery. In pulmonary stenosis and atrial septal defect, the maximum frequency of the murmur created in the pulmonary artery reaches the chest wall. The former has frequency components greater than those seen in the normal.

Thebesian Drainage in the Left Heart of the Dog: The Left Anterior Atrial Artery (P)

Thomas W. Moir, Thomas E. Driscol, and Richard W. Eckstein, Cleveland, Ohio

Isotope (I^{131} albumin) injection into the left circumflex artery of the dog consistently results in early appearance of radioactivity at sampling sites in the left heart and aorta. Occlusion of the left anterior atrial artery, a branch of the circumflex supplying the left atrial appendage, during such injections causes obliteration or attenuation of these early peaks of radioactivity. This finding is consistent with direct left-heart drainage of the circumflex artery via the left anterior atrial artery.

Estimates of the magnitude of such drainage have been made in dogs with the heart beating in situ with normal pressure-flow relationships. With the circumflex artery cannulated and perfused above the origin of the left anterior atrial artery, small volumes of high specific activity I^{131} albumin have been injected into the cannula tubing and time-concentration curves recorded from the root of the aorta. Simultaneous determination of cardiac output with indocyanine green dye has permitted the calculation of the amount of left heart drainage represented by the time-concentration curves of radioactivity; an average of 5 per cent (range 3.7 to 7.0) of circumflex outflow drains into the left heart, the majority via the left anterior atrial artery.

Preliminary direct study of the left anterior atrial artery by the same technic has shown that, with an average metered inflow of 4.4 ml./ min., 72 ml./min./100 Gm. left atrium, approximately 40 per cent of outflow drains into the left heart.

Ebstein's Anomaly, a Cause of Massive Cardiomegaly in the Newborn Infant

Marion E. Molthan, Alois R. Hastreiter, and Robert A. Miller, Chicago, Illinois

It is not generally recognized that Ebstein's anomaly may produce massive cardiac enlargement and diminished pulmonary blood flow in the newborn infant. Severe pulmonary valvular stenosis or atresia, which may require emergency surgery in the first days of life, is usually associated with tricuspid insufficiency and stenosis, making differentiation from Ebstein's anomaly important.

Two cyanotic infants were examined within the first 24 hours of life. Each had a very large heart, a pansystolic murmur with a faint thrill at the left sternal border, a mid-diastolic murmur, diminished intensity of the second sound, and congestive failure. One had a pulsating liver. The electrocardiograms showed right axis deviation, incomplete right bundle-branch block, and right atrial hypertrophy. Cardiac catheterization in 1 infant, at 3 and at 13 days of age, showed low right atrial pressure, right ventricular pressure of 40/2, and a right-to-left shunt at the atrial level. The cineangiocardiogram showed an intact ventricular septum and marked tricuspid regurgitation. The pulmonary artery was not well visualized. Both infants were operated upon; both were subsequently shown to have Ebstein's anomaly at autopsy.

The electrocardiograms in these 2 patients, although not typical of Ebstein's anomaly, showed more block and less right ventricular hypertrophy than is usually present in severe pulmonary valvular stenosis at this age.

The similarity of the clinical and physiologic findings of tricuspid insufficiency alone to those of combined tricuspid and pulmonary valve lesions of the newborn makes selection of infants for emergency surgery more difficult.

Left Ventriculography for the Determination of the Size, Location, and Associated Anomalies in Patients with Ventricular Septal Defect

Rogelio Moncada, Juan Pedro Bicoff, Rene A. Arcilla, Benjamin M. Gasul, and Zwi Steiger, Chicago, Illinois

Twenty-three children with ventricular septal defects, 6 months to 14 years of age, had retrograde left ventriculography. Five patients had associated congenital malformations: mitral regurgitation in 2, atrial septal defect in 2, and coaretation of the aorta in 1. The biplane angiocardiograms (8 per second in each plane) always demonstrated a stream of contrast substance passing through the defect into the right ventricle. The area of the defect was determined using the following formula:

$$S_t = \frac{C_t \cdot S_a}{C_a} \quad \text{Area} = \left(\frac{S_t}{2}\right)^2 \cdot \pi$$

where: S_t = diameter of defect, C_t = true diameter of catheter, S_a = diameter of shunt, and C_a = diameter of the catheter in the angiocardiogram.

The areas of the defect varied from 7.8 $mm.^2$ to 2.86 $cm.^2$ The size of the defects varied during the various phases of the cardiac cycle up to 33 per cent. In the uncomplicated cases, it appeared to correlate with the pulmonary pressures and flows obtained on cardiac catheterization. In 4 patients in whom routine cardiac catheterization did not reveal a shunt, the left ventriculograms showed small shunt streams of 2.6 to 5.4 mm. diameter. Low muscular defects were present in 3 patients, of whom 1 had an additional tiny membranous defect. Aneurysm of the pars membranacea was demonstrated in 2 patients, mitral regurgitation

in another 2, and coaretation of the aorta in 1. The procedure is relatively easy and safe. It is useful for demonstrating the size, location, and number of defects and the presence of other complicating anomalies. It appears to be more sensitive than routine cardiac catheterization for demonstrating very small ventricular septal defects.

Heart Disease and Alcoholism

Robert R. Morgan, New York, New York

The association of heart disease and cirrhosis has been tabulated in 265 cirrhotic patients at the St. Vincent's Hospital of the City of New York. It has been stated that there is a diminished incidence of heart disease in those with cirrhosis of the liver. This is attributed to increased circulating estrogens and an increase in the clearing factor lipoprotein lipase, as well as to increased plasma fibrinolysin. On the other hand, chronic heart failure due to beri-beri, or multiple vitamin deficiency, with "nutritional heart disease" has been described.

In the present series there were 226 cases of nutritional or Laennec's cirrhosis associated with severe alcoholism. The coronary arteries were serially section in 239 hearts. Sign of atherosclerosis was absent in 73 (30 per cent), minimal in 77 (32 per cent), moderate in 60 (25 per cent), and marked in 23 (10 per cent). Coronary occlusion was found in only 6 (2.5 per cent).

Heart weights were recorded in 240 cases. In these, 133 weighed less than 400 Gm., 66 weighed between 400 and 499 Gm., and only 42 weighed 500 Gm. or more.

Hypertensive heart disease was present in 12 patients with enlarged hearts and 2 patients had rheumatic heart disease.

ECG evidence of myocardial hypoxia was present in 35 cases. Congestive heart failure was present in 11 cases.

The distribution of heart disease as seen in this large group of alcoholic patients probably represents nothing more than the distribution of heart disease in any group of patients with severe chronic disease in the same age group.

Paroxysmal Atrial Tachycardia with Block Treated with Digitalis

William L. Morgan and Gerald M. Breneman, Detroit, Michigan

It is an accepted fact that digitalis is frequently the cause of paroxysmal atrial tachycardia with block (P.A.T.B.). This arrhythmia occurred in 14 patients in a 1-year period. In 5 patients it was caused by digitalis. Nine others, however, did not have digitalis intoxication but required digitalis to control congestive failure or the rapid ventricular rate.

Three of these 9 patients had received no prior digitalis and were subsequently digitalized. This included the only case without heart disease but with intermittent P.A.T.B. for 5 years. Two patients with mitral stenosis developed P.A.T.B. on maintenance digitalis in the absence of diuretics. The arrhythmia was unaffected by stopping the drug and adding potassium. After redigitalization both converted to sinus rhythm. After modest digitalization 2 additional patients developed the arrhythmia transiently for 2 and 4 days respectively, despite no change in diuretic or digitalis maintenance therapy. The remaining 2 patients showed electrocardiographic features intermediate between P.A.T.B. and atrial flutter. One with an atrial rate of 260 and isoelectric intervals was converted to sinus rhythm with additional digitalis. The other with an atrial rate of 214 but broad inverted P waves in the posterior leads maintained the rhythm a full year.

Digitalis excess should be considered in any case of P.A.T.B. Should the arrhythmia persist after stopping digitalis and adding potassium, the cautious addition of more digitalis may be indicated.

Open vs. Closed Surgery for Mitral Stenosis

D. P. Morse, T. R. Keith, and M. Ramundo, Passaic, New Jersey

The advent of extracorporeal circulation has now made possible an improved operation for mitral stenosis. The authors compare their experience in the last year with the open technic with that in the preceding 5 years using the closed technic. The technical operative advantages include routine full opening of the valve, removal of all valve calcification or loose atrial clots which with closed surgery form emboli, the ability to correct any pre-existing mitral insufficiency, and the power to prevent the creation of new insufficiency which occurred to a significant degree in approximately 6 per cent of the closed cases. The mortality at the Passaic General Hospital has been as low as that with the closed technic.

The improvement in the operated has been reflected in the postoperative clinical results. For the first time, the majority of the patients have no murmurs, either systolic or diastolic, postoperatively; there is increased tendency toward diminution of the heart size by x-ray and the electrocardiographic changes toward normal are striking. The functional improvement in the patient in every way can be noted to a greater extent in those patients operated under direct vision.

Effect of Heparin upon Thrombolytic Activity of Fibrinolytic Agents in Vivo: Preliminary Report

Kenneth M. Moser, Steven B. Sulavik, and George C. Hajjar, Washington, D. C.

In vitro observations have indicated that heparin, in proper concentration, may potentiate the thrombolytic activity of fibrinolytic agents. To determine whether such potentiation also occurs in vivo, thrombi were formed in both jugular veins (Wessler method) in 18 dogs. One thrombus was exposed to circulating blood, the other isolated between ligatures. Three dogs served as nontreatment controls; 3 received 1 intravenous dose of heparin (1 mg./Kg.); 8 received a streptokinase-plasminogen (activator/plasmin) mixture intravenously, according to a predetermined sequence of variation in total dosage and duration of infusion; 4 received heparin plus fibrinolytic agent. Predicted dose tests (Sherry) were carried out before treatment. Determinations of plasma recalcification time, prothrombin time, fibrinolytic activity (euglobulin and fibrin plate methods), and fibrinogen were made before and during control and treatment periods. Both jugular vein segments were removed intact after 4 to 6 hours of observation.

The isolated thrombus was found to remain intact in all dogs at the end of 4 to 6 hours. In control and heparin-treated dogs the "exposed" thrombus remained intact. In dogs treated with fibrinolytic agent alone, administration of the total predicted dose (TPD) in 15 to 30 minutes altered coagulation and fibrinolytic parameters but did *not* induce thrombolysis; however, when given over 4 hours, doses 75 per cent or more of the TPD consistently induced complete thrombolysis. Thrombolysis was *not* obtained when less than 75 per cent of the TPD was administered alone. However, in heparin-fibrinolytic dogs, thrombolysis consistently occurred at doses of fibrinolytic agent that were ineffective in the absence of heparin.

Total Prosthetic Replacement of the Diseased Aortic Valve (P)

William H. Muller, Jr., James B. Littlefield, and J. Francis Dammann, Jr., Charlottesville, Virginia

Total subcoronary prosthetic replacement of the aortic valve has been performed in 21 patients. Eleven patients have progressed satisfactorily from 1 week to 13 months since operation. Aortic insufficiency was the predominant lesion in these patients although aortic stenosis or a combination occurred in some. Left-heart catheterization demonstrated either severe aortic insufficiency with a markedly elevated end-diastolic pressure or a high gradient across the valve. These patients were severely ill, and, at the time of operation, total prosthetic valvular replacement was mandatory because valvular repair could not be accomplished. Continuous left coronary-artery perfusion was used in the majority of patients, but right coronary-artery perfusion was also performed in those more recently operated upon.

All of the valvular prostheses except one were constructed entirely of Teflon. The initial prostheses were made of a thin-walled cylindrical cage, covered outside with coarse netting to permit ingrowth of fibroblasts; the interior, highly polished, contained 3 knitted leaflets (100 denier) securely sewn to the cage. In the current modified prostheses, the cylindrical cage has been eliminated; the leaflets are tightly sewn together laterally and a roll of fabric at the base is sutured to the annulus. The commissures are individually sutured to the aortic wall. Thrombus formation and embolization have not occurred in any of the patients. Catheterization studies indicate that the teflon prosthesis functions well. Postoperative studies have been made.

Changes in Blood Coagulation and Fibrinolysis in the Presence of Dietary-Induced Lipemia (P)

Shapur Naimi, Robert Goldstein, Martin M. Nothman, George F. Wilgram, and Samuel Proger, Boston, Massachusetts*

The connection between lipemia and clotting changes in vitro has been a subject of much controversy, and the relevance of all this to the mechanism of thrombosis in vivo remains unsettled. A suitable experimental model to appraise the interrelationship among these parameters seemed to be provided in the recent reports of induction of vascular thrombosis and myocardial infarction in the rat.

Two groups of rats, each consisting of 40 Wistar albinos, were studied. The diet of 1 group included cholesterol, sodium cholate, propylthiouracil, and 40 per cent butter. The other group was fed on fox chow and acted as normal controls. In the diet group, lipid studies showed grossly elevated cholesterol, phospholipids, total fatty acids, and phosphatidyl ethanolamine and serine. Pathologic studies confirmed the reports of increased tendency to thrombosis and infarction in this group, although the exact pathologic nature of these lesions is yet to be determined. In vitro studies showed a statistically significant increase in coagulation activity as indicated by the thromboplastin generation test, prothrombin time (Quick), determinations of prothrombin and Factor VII, and stypven time. Fibrinolytic activity on the other hand was reduced. Conversely, preliminary observations in another group on 40 per cent butter alone, which in rats causes obesity but no pathologic lesions apart from minimal fatty streaking, showed no significant lipid or coagulation changes. It, therefore, appeared reasonable to assume an association among the 3 parameters:

lipemia, clotting changes in vitro, and thrombosis in vivo. Finally these conclusions should be considered in the light of the limitations imposed by the nature of these experiments.

Possible Significance of Water Movement Across Skin and Urinary Bladder in Heart Disease

William A. Neely, William C. Garre, Manson D. Turner, and Joseph D. Smith, Jackson, Mississippi

Transfer of water from a humid atmosphere through skin into the circulatory system appears to be important in the management of congestive failure. Infants in congestive failure may be extremely sensitive to humid atmospheres provided by many "so-called" croupettes. Absorption of water through the urinary bladder could be important in cardiacs because they are in the older age group in which urinary retention may be a problem. To evaluate this problem, the authors have undertaken this study.

An air-tight metal chamber was constructed with a suitable nebulizing system so as to maintain a saturated atmosphere in D_2O about a dog except the head. D_2O was also injected into isolated urinary bladders (100 Gm. in patients, 50 Gm. in dogs). By plotting the hourly concentrations of D_2O in plasma against time, we were able to measure the amount transferred per unit time and per unit of surface area and/or weight.

In 8 dogs studied, 46 $\pm$ 8 Gm. of D_2O per square M. per hour moved across the skin into the body-water pool. Only about one-half to two-thirds of this amount was found to move in the opposite direction. In 5 patients 11.3 $\pm$ 1.9 Gm. of D_2O passed through the human bladder per 70 Kg. man per hour. In 10 dogs 8.35 $\pm$ 6.5 Gm. of D_2O crossed the bladder-body water barrier. The rate of movement in the dog bladder was much higher than in the human bladder. There was more variability to the movement of D_2O through the animal bladder. Studies on infants are in progress.

Outcome of Pregnancy in Congenital Heart Disease (P)

Catherine A. Neill and Sheila Swanson, Baltimore, Maryland

As part of a study of familial and genetic factors in congenital heart disease a questionnaire was sent to 1,000 patients over 18 years of age who had formerly attended the Harriet Lane Home Cardiac Clinic. Replies were received from 704 patients (328 males, 376 females) of whom a total of 336 were married and 235 had conceived. The results of the 508 resulting pregnancies were analyzed to determine if there was a higher than normal incidence of congenital heart disease among the offspring and to determine if the results of pregnancy varied between the different diagnostic groups.

The 508 pregnancies resulted in 122 miscarriages, 22 perinatal deaths, 7 live-born children with congenital heart disease, 8 live-born with other malformations and 349 normal children: thus 68 per cent of all pregnancies resulted in normal children, while 1.8 per cent resulted in offspring (including live born and perinatal deaths) with congenital heart disease (approximately 6 times the "normal" incidence).

The patients with conotruncus malformations (tetralogy, etc.) had the lowest incidence of normal children. Further breakdown revealed an extremely high incidence of spontaneous abortion in cyanotic mothers, an incidence which reached 80 per cent of all pregnancies when the mother's hematocrit was 65 or more, and was 60 per cent even in the mildly cyanotic mothers. Moreover, when born alive, the offspring of the cyanotic mothers were unusually small, with a mean birth weight of about 5½ pounds. The mean birth weight of the children of the cyanotic fathers was 7 pounds 6 ounces or normal. These observations suggest that the presence of cyanotic heart disease affects fetal intrauterine nutrition.

Persistent Myocardial Hyperemia and Increased Oxygen Consumption During Recovery from Exercise in Man

William A. Neill, Norman Krasnow, Richard J. Wagman, Herbert J. Levine, and Richard Gorlin, Boston, Masachusetts

Left ventricular (LV) coronary flow (CF), oxygen consumption (qO_2), work, and tension time index (TTI) were determined in 37 patients at rest and during a 7-minute exercise and during a 4-minute recovery period starting 1 minute after the end of exercise. Exercise work and TTI increased more than qO_2, and efficiency rose significantly in over 50 per cent. Although LV hemodynamics had returned to near rest levels, recovery CF and qO_2 remained significantly elevated in 73 per cent. Recovery hyperemia appears to be related to the degree of LV stress during exercise. Ten of 12 patients with greatly elevated recovery CF (+50 to +200 per cent) had comparably increased exercise CF and abnormally increased LV work owing to heart disease. The remaining 2 had excessively increased exercise TTI but no rise in CF until recovery. Twelve patients with intermediate increase in recovery CF had comparable changes in CF and LV stress during exercise. Virtually no recovery changes occurred in the group with minimal effort stress. Recovery

hyperemia was not accompanied by narrowed oxygen extraction. In the 3 patients with largest exercise fall in coronary venous oxygen saturation, saturation remained low through recovery, suggesting persistent oxygen needs out of proportion to CF. Average efficiency was higher during exercise (+30 per cent) and lower during recovery (−13 per cent). At least part of the apparent increase in exercise efficiency may represent utilization of anaerobic or stored energy, requiring oxygen for postexercise restoration. No excess lactate production during exercise has been demonstrated.

Measurement of Circumferential Thorax Potentials during Successive 1-msec. Intervals

Clifford V. Nelson, Portland, Maine*

An analyzer for the electrocardiogram and other bioelectric potentials has been developed. The instrument records automatically the potential distribution around the thorax during successive 1-msec. intervals. The 20 thorax electrodes are connected to 20 preamplifiers. Each amplifier output is connected through a gate circuit to a common output line. The gates are turned on in succession by an electronic commutator. Each gate on time is 50 μsec., and a complete scan from all electrodes is made in 1 msec. The object of this report is to show the kind of results which are being obtained from one complete channel of the analyzer.

The composite output signal is applied to an Ampex FR-1100 magnetic tape recorder. This recorder was designed to provide a playback to record speed ratio of 1 to 128. A speed ratio of 1 to 512 has been used with no apparent loss of information. The slowed-down data is applied directly to a Sanborn Model 320 hot stylus recorder. If this unit is run at 1 mm./sec., a "histogram" of the response during the entire heart cycle is obtained. At a speed of 100 mm./sec., each 1 msec. graph of potential occupies about 5 cm. on the record. The results obtained so far have fully satisfied our original specifications.

Critical Evaluation of the Effects of Procaine Amide on Ventricular Fibrillation Threshold

Russell M. Nelson, James W. Henry, and C. Gordon Frank, Salt Lake City, Utah

The use of procaine amide in the treatment of cardiac arrhythmias and in the prophylaxis against arrhythmias in patients undergoing cardiac surgery has been advocated by some investigators. The work to be reported was carried out in an effort to assess critically any possible effect of procaine amide on cardiac irritability as measured by this technic.

Ventricular fibrillation threshold was determined in open-chest dogs by measuring the milliamperes of current required to produce ventricular fibrillation with a shock of 10-msec. duration delivered via electrodes placed in the heart. The shock, electronically triggered by the R wave of the electrocardiogram, was timed by a delay circuit to occur at the apogee of the T wave. This portion of the cardiac cycle is the time at which the heart is most vulnerable to ventricular fibrillation. This threshold has been found to be valid and reproducible. Temperatures were carefully controlled and heart rates were controlled by driving the heart at constant rates with an internal pacemaker.

Procaine amide was administered in 46 experiments to 16 dogs in dosages ranging from 5 mg./Kg. to 20 mg./Kg. Ventricular-fibrillation thresholds were determined serially after each injection.

Results revealed that there was no statistically significant alteration in ventricular-fibrillation threshold after the intravenous administration of procaine amide. The occasional elevations in threshold that were found fell within the range of probability of occurring by chance alone.

Syndrome of Congenital Cardiac Disease with Asplenia: Distinction from Other Forms of Congenital Cyanotic Disease (P)

Henry N. Neufeld, Russell V. Lucas, Jr., Paul Adams, Jr., Richard G. Lester, Ray C. Anderson, Minneapolis, Minnesota, and Jesse E. Edwards, St. Paul, Minnesota

The syndrome of congenital absence of the spleen and congenital cardiac disease is important because of its limited therapeutic potential and poor prognostic implications in contrast to that which pertains in other forms of cyanotic congenital cardiac disease.

A study which leads to a basis for distinction between these 2 categories was derived from observation of 14 necropsy-proved cases of asplenia and congenital cardiac disease.

Clinical, electrocardiographic (9 cases), and angiocardiographic (8 cases) findings were correlated with the pathologic.

A universal anatomic finding not previously emphasized was an abnormal relationship of the great vessels to each other and to the heart as seen in corrected transposition of the great vessels. All but 1 case showed a persistent common A-V canal and partial or complete obstruction to pulmonary arterial flow was present in each. In half of the patients, isolated or situs inversus dextrocardia was present. Anomalies of pulmonary venous and systemic venous connection were common. The condition of "bilateral right-side-

ness," as evidenced by bilateral trilobed lungs, symmetrical liver, and asplenia, was common to all cases.

The complexity of the cardiac malformations in the asplenic syndrome usually precludes application of those curative surgical procedures that are applicable in other types of cyanotic congenital disease. Separation of cases with the cardiac anomalies with more favorable therapeutic potential include (1) radiologic evidence of hepatic symmetry, (2) electrocardiographic features of the "A-V commune" type, (3) transposition of vessels, and (4) hematologic signs of asplenia.

Epidemiologic Studies on Cardiovascular Diseases in Charleston County, South Carolina: Mortality Analysis by Age-Race-Sex

Milton Z. Nichaman, Edwin Boyle, Jr., Thomas P. Lesesne, Columbia, South Carolina, and Herbert I. Sauer, Washington, D. C.

A race-sex-age analysis was made of mortality due to the major cardiovascular disease in Charleston County, South Carolina, for the years 1955 to 1958. Over one-third of the population of this area are Negroes who have been shown in previous anthropologic studies to be much more closely related to the African Negro than to the American Negro. Principal findings of the analyses are as follows: (1) Negro males had death rates due to arteriosclerotic heart disease (ASHD) almost as high as that found in white males (0.78:1), while Negro females had higher rates than were found in white females (1.4:1). (2) The sex differential for ASHD in whites was quite marked with the ratio being 4.6:1 for males to females, while the ratio for the Negroes was 1.4:1. (3) Hypertensive disease was found to be much more common in the Negro with the ratios being 7:1 for males and almost 10:1 for females. (4) Cerebral vascular disease similarly was found to be more prevalent in Negroes with ratios of 5:1 for males and 11:1 for females. (5) Deaths from all cardiovascular diseases were shown to decrease in the Negro after age 65.

A detailed comparison of the results shows close agreement with similar data from other parts of the United States with the exception of very high Negro death rates for hypertensive and cerebral vascular disease. The age distribution for deaths due to all cardiovascular disease showed that the Negro males died 15 years younger than the white males, while the Negro females died 20 years younger than the white females.

Open-Heart Surgery for Mitral Stenosis and Mitral Regurgitation (P)

Henry T. Nichols, Gumersindo Blanco, and Joseph F. Uricchio, Philadelphia, Pennsylvania

Experience with the first 200 patients operated upon for mitral stenosis and regurgitation by an open technic is presented. A left thoracotomy approach to the mitral valve was employed in each case. Of these, 120 (60 per cent) had isolated mitral stenosis. In 20 (10 per cent), surgery was performed on the mitral valve for restenosis. The overall mortality for the "stenotic group" was 9 per cent.

Sixty (30 per cent) had mitral regurgitation. Noncuspal disease (dilated annulus and ruptured chordae) was encountered in 8 (4 per cent). The overall mortality for the "regurgitation group" was 13 per cent.

The advantages of open-heart surgery in the treatment of rheumatic mitral-valve disease is discussed. The extraction of large atrial clots and removal of calcific plaques can only be accomplished by this type of surgery.

Long-term results were analyzed by cardiac catheterization, cineradiography, cardiac ventriculography, and phonocardiography. The results strongly favor abandonment of "closed procedures" for the treatment of these lesions.

Postmortem Coronary Perfusion, Angiography, and Resection (P)

Nelson R. Niles and Charles T. Dotter, Portland, Oregon

Occlusive disease was assessed in 160 cases by use of postmortem coronary-artery perfusion and angiography. Collateral circulation was measured and was variable but present in all types of cases. Correlation of these data with results of subsequent injection of opaque latex and examination a la Schlesinger was made. Occlusive disease was demonstrably most frequently segmental and in proximal and larger arteries and was therefore theoretically amenable to operative resection. Complexity of arterial branching, errors in evaluation of angiograms, and the occasional extensive distribution of the disease were recognized as hindrances to beneficial resection.

Arterial resection has been attempted in 8 hearts on the basis of perfusion data and angiograms. Perfusion rates have been significantly increased (more than 10 per cent) in 4 cases and not significantly changed in 1. In 3, either a decrease has resulted or there has been a significant operative leak.

With accumulating experience in angiographic interpretation and in operative technic, cases can be more accurately selected for resection and results improved.

The study is continuing. Investigation of various methods of removal of arterial obstructions is in progress.

Use of Digitalis in Chronic Complete Atrioventricular Heart Block: A Critical Experimental Study

Paul M. Nonkin, Louis D. Bennett, and Fred Wasserman, Coral Gables, Florida

There is controversy and some confusion concerning the use of digitalis in the presence of chronic complete A-V heart block; in part, this has resulted from technical limitation for critical experimentation in the intact animal.

Utilizing the Magarus modification of the Hatcher-Brody method of bioassay, we studied tolerance to digoxin in normal mongrel dogs and in dogs with surgically induced chronic complete atrioventricular heart block. An irrefutable end point of digitalis cardiotoxicity, the lethal dose, was compared.

The mean lethal dose of digoxin in animals with chronic complete A-V heart block was 0.319 mg./Kg.; normal control dogs developed terminal ventricular fibrillation or standstill after 0.293 mg./Kg. There was no significant difference in tolerance between the two groups.

The electrocardiographic signs of cardiotoxicity were observed in both groups of animals after the administration of 40 to 85 per cent of the lethal dose of digitalis. In animals with complete heart block the electrocardiographic manifestations differed from those usually associated with digitalis.

Diagnosis of Rheumatic Heart Disease in Patients with No History of Acute Rheumatic Fever

Jacqueline A. Noonan and John C. McQueen, Iowa City, Iowa

Since 1954 approximately 850 patients, all under 21 years of age, have been enrolled in a statewide penicillin prophylaxis program for the prevention of recurrences of rheumatic fever. All are followed regularly affording a good opportunity for observing the natural history of rheumatic heart disease. Four hundred seven patients or about half of the total enrolled, have continued to have evidence of rheumatic heart disease; 27 (7 per cent) of this number presented with heart murmurs very suggestive of rheumatic heart disease with no known history of acute rheumatic fever. The possibility of congenital heart disease was fairly well excluded by appropriate studies and the past history of the previous absence of murmur.

The distribution of the various valvular lesions was similar for each group except for isolated mitral stenosis. Four of the 14 patients with mitral stenosis were in the group having no history of rheumatic fever. Mitral insufficiency was the predominant lesion in both groups and accounted for two-thirds of the valvular lesions present. It was of concern to note that the majority of the 27 patients had evidence of quite severe valvular involvement. Two patients have required a mitral valvotomy at ages 9 and 14 years, and surgical correction of severe mitral insufficiency is planned in another.

Rheumatic carditis must occur without other systemic symptoms sufficient to cause concern and still lead to severe valvular disease. Heart murmurs in this group were usually noted at a routine physical examination except for a few, when cardiac symptoms directed attention to the heart. Late murmurs have not occurred in patients previously free of abnormal heart findings in our experience. The finding of rheumatic heart disease, especially mitral stenosis, in adults without a history of rheumatic fever is well known. Our experience suggests that rheumatic fever with carditis may occur and be unrecognized in childhood and result in serious valvular involvement that goes unnoted until symptoms occur.

Effect of Anoxic Stress at 31 and 37 C. upon the Adenosine Triphosphate Content of Human Cardiac Muscle

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Human auricular muscle was obtained at time of cardiac bypass and immediately immersed in oxygenated Krebs' solution at room temperature. Intact muscle bundles were then dissected free and mounted in a muscle chamber. Stimulation of the muscle was accomplished by a square wave stimulator and contractions recorded on an electric kymograph by an ink-writing pen. Anoxia was provided by bubbling nitrogen through the Krebs' solution.

Adenosine triphosphate (ATP) was analyzed by the combined enzymatic and spectrophotometric method of Kalckar.

Twenty human cardiac muscle strips were analyzed for ATP under the following conditions:

The protective effect of hypothermia during anoxia was shown by the response of 4 human muscle strips that had been anoxic for 30 minutes at 31 C. and then permitted to recover in an aerobic atmosphere. The ATP content of these muscles was the same as that of 7 muscle strips that had been analyzed prior to stimulation and 3 muscle strips after 90 minutes of aerobic stimulation at 37 C. In contrast, 6 muscle strips, exposed to anoxic stress of 30 minutes at 37 C. and allowed 30 minutes of recovery, showed a 47 per cent decrease in ATP content when compared with the control levels. The pattern of contractile response of the muscle strips paralleled that of the ATP content. Recovery of contractile force

after anoxia at 31 C. was complete, whereas recovery following anoxia at 37 C. was 50 per cent of the control.

Similar results were obtained with the left atria of 30 guinea pigs.

The results demonstrate the protective effect of hypothermia during anoxia upon recovery of contractile strength and the preservation of the ATP content of human and guinea-pig atria muscle.

Diagnostic Signs of Myocardial Infarction in the Presence of Complete Left Bundle-Branch Block (P)

Robert J. Norris and Ralph C. Scott, Cincinnati, Ohio

Twenty electrocariographic criteria previously advocated as helpful in the diagnosis of myocardial infarction complicating complete left bundle-branch block (LBBB) have been studied. These criteria were applied to 52 cases of LBBB, all with necropsy verification. The cases were subdivided into a control group of 29 free of infarction and 23 constituting the infarction group.

With the exception of Q waves (of any size) in V_6 or Q waves of 0.04 second or greater in I, aV_L, or V_5, most criteria were found to be nonspecific. Q waves in lead I, long thought to be the hallmark of septal infarction, were present without infarction in 14 per cent of the control group and in 14 per cent of the infarcted group without septal involvement and in 22 per cent when the septum was involved.

Of the remaining criteria considered applicable to anteroseptal infarction, only a few appeared to be of value. The late notching of the S wave in V_3 and V_4 described by Cabrera, with 22 per cent incidence in the infarction group, showed a high degree of specificity. Of a lower order of specificity were notched S waves in V_4 as described by Chapman and Pearce, abnormal R-wave progression in precordial leads, and rsR′ patterns in I, aV_L, and V_6.

The criteria for pure septal infarction and for inferior infarction proved to be entirely nonspecific in our case.

Additional criteria recently suggested by Besoáin-Santander and Gómez-Ebensperguer were found to be of equivocal value.

Attempts to correlate the various electrocardiographic criteria with necropsy data as to the size of the infarction, its age, or localization were completely unsuccessful.

The electrocardiographic diagnosis of myocardial infarction complicating LBBB is difficult but may be suspected when one or more of the following patterns occur: (1) Q waves of 0.04 second or greater in I, aV_L, V_5 or V_6; (2) rapid serial S-T segment and T-wave changes; (3) acute S-T segment elevation disproportionate to the area of the QRS complex; and (4) a Q wave (of any size) in V_6.

Effect of Diet Alone and in Combination with Unsaturated Fatty Acids on the Plasma Cephalins in Normal Subjects and in Patients with Coronary Heart Disease (P)

Martin M. Nothman and Samuel Proger, Boston, Massachusetts

Last year we reported that in patients with hyperlipemia and hypercholesterolemia and in those with coronary heart disease, the values for phosphatidyl ethanolamine and serine are 2 to 3 times as high as in normal individuals. The effect of diet alone and in combination with unsaturated fatty acids on cephalins has been investigated. For determination of the cephalins the method of Axelrod, Reichenthal, and Brodie has been used. Five normal individuals, 10 patients with myocardial infarction, 5 patients with hypercholesterolemia but without myocardial infarction, and 3 patients with hyperlipemia, hypercholesterolemia, and xanthomatosis were studied. In normal individuals on a low animal-fat diet, phosphatidyl ethanolamine fell within 1 to 2 months about 10 per cent from the original values, which were between 3.5 and 6.4 mg. per cent. In hypercholesterolemic patients, with or without myocardial infarction, the values for phosphatidyl ethanolamine decreased from between 11.4 mg. per cent and 40.72 mg. per cent to from 9.2 to 33.9 mg. per cent; that is, there was a reduction of from 5 per cent to 25 per cent with diet alone. When unsaturated fatty acids were added, the values fell 35 per cent to 55 per cent additionally and reached normal or almost normal levels. Phosphatidyl serine fell in normal subjects about 12 per cent with diet; in hypercholesterolemic patients there was a drop from between 17.0 and 49.84 mg. per cent to between 14.3 and 41.8 mg. per cent, that is, from 8 per cent to 28 per cent with diet alone and from 29 per cent to 60 per cent when unsaturated fatty acids were added.

The investigations suggest that a low animal-fat diet will reduce the cephalins in plasma by about 25 per cent of their original value. When a mixture of linoleic, linolenic, and arachidonic acids is added to the diet, the reduction will become 2- to 3-fold.

Experiences with Transeptal Catheterization of the Left Heart

Paul Novack, Fernando E. A. Mendoza, Diego DeArmas, Hratch Kasparian, and William Likoff, Philadelphia, Pennsylvania

The Ross method of left-heart catheterization has been employed in the study of 84 patients with mitral and aortic valvular disease. The left atrium was entered in 95 per cent of the cases and the left ventricle in 83 per cent. On 3 occasions the catheter could not be advanced beyond the femoral-iliac vein junction. In 5 instances it was possible to advance the polyethylene catheter into the aorta, although no attempt was made to accomplish this routinely. In 82 of the cases right-heart catheterizations were performed through the same vein (saphenous). The pulmonary artery was entered in 75 per cent of the cases and in the remaining instances the right ventricle was entered. There were no fatalities. Morbidity was confined to an occasional wound infection. In 1 case a short segment of polyethylene catheter was subsequently found in the left atrium at the time of surgery. Hemopericardium was not noted at time of cardiotomy. The procedure is better tolerated by the patient than are the transthoracic and transbronchial approaches. The Ross needle may be left in the atrium for relatively long periods allowing for the completion of more prolonged studies. The overall degree of success in obtaining the pertinent data is as good as with other methods. This experience leads us to conclude that this technic is the procedure of choice for left-heart catheterization.

Assessment of Regurgitation by Dye-Dilution Curves

Paul Novack, Fernando E. A. Mendoza, Diego DeArmas, Bernard L. Segal, and William Likoff, Philadelphia, Pennsylvania

According to Lange and Hecht, differences in the contour of indicator-dilution curves recorded from the pulmonary artery and the femoral artery reflect the presence of mitral or aortic insufficiency. In 42 patients with mitral and aortic valvular disease we have analyzed curves obtained by consecutive sampling from the pulmonary and brachial arteries after injection of indocyanine green into a peripheral vein. The difference between mean transit time and appearance time for the brachial-artery curve and the corresponding value for the pulmonary-artery curve provided the most consistent correlation with other findings. In 15 cases where this difference was 8 seconds or greater, significant degrees of regurgitation were confirmed by selective left ventricular angiography in 6, by surgery in 5, and by clinical and catheterization criteria in the remaining 4 cases. In 27 patients in whom the difference was less than 8 seconds, the absence of significant regurgitation was established by clinical and catheterization findings in 13, by surgery in 11, and by ventriculography in 1 case. In 2 instances the dye curves failed to indicate the presence of major mitral insufficiency, which was not only clinically apparent but was subsequently visualized by ventriculography. We have concluded that angiography must be considered the most reliable means to demonstrate valvular insufficiency. Our past experience with other methods suggests that this dual curve approach is the best of the dye-dilution procedures for detecting and evaluating the significance of valvular regurgitation; however, all such methods are inherently subject to occasional gross failure for reasons not immediately apparent.

Regulatory Mechanisms of Pulmonary Blood Volume in Mitral-Valve Disease (P)

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Patients were studied during investigation by simultaneous right-heart and transseptal left atrial catheterizations. All patients had significant mitral-valve lesions. Dilution curves were recorded from a systemic artery after injections into the pulmonary artery (PA) and the left atrium (LA). These were either simultaneous injections of 2 indicators, Cardiogreen and I^{131} radioiodinated human serum albumin, or rapidly successive injections of 1 indicator, Cardiogreen. Pulmonary blood volume (PBV) was calculated from the difference between the 2 mean transit times multiplied by the cardiac output. The mean intravascular pressure (P_i) acting to distend the pulmonary vessels was taken to be the average of the mean PA and LA pressures $(\bar{P}_{PA} + \bar{P}_{LA})/2$.

In a series of 18 patients PBV at rest ranged from 140 to 503 ml./M.^{2} with a mean of 295 ml./M.^{2} The difference on duplicate determinations of PBV in 10 patients was 12.3 ± 8.3 ml./M.^{2} BSA (mean ± S.E.).

The effects of infusion of acetylcholine, angiotensin, and hexamethonium on PBV and $\bar{P}_i$ were determined. Acetylcholine increased PBV with no change or a decrease in $\bar{P}_i$. This increased vascular capacity in the face of diminished distending pressure implies active pulmonary vasodilatation. Conversely, angiotensin lowered PBV with no change or an increase in $\bar{P}_i$ indicating active vasoconstriction. Hexamethonium had the same effect as vasovagal reactions and caused a concomitant reduction of both PBV and $\bar{P}_i$, attributed to passive narrowing of pulmonary vessels resulting from pooling of blood outside the thorax.

These studies give evidence of both active and passive mechanisms of pulmonary blood-vessel regulation.

Blood-Pressure Response to the Valsalva Maneuver in Patients with Atrial Septal Defects

G. Charles Oliver and Herbert N. Hultgren, Palo Alto, California

In this study the effects of a left-to-right shunt at the atrial level upon the response to a Valsalva maneuver were investigated to determine whether this technic could be used as a simple screening test for the presence of an atrial septal defect (ASD). During the course of right-heart catheterization, the blood-pressure response to a standard Valsalva was recorded, using an intra-arterial needle and a strain-gauge manometer in a group of 16 patients with ASD's and the results compared with a group of 10 hemodynamically normal subjects. An attempt was made to establish objective criteria for evaluating the blood-pressure response, and a Square Wave Index was devised for this purpose. This index is the lowest systolic pressure measured during the strain, minus the systolic pressure recorded immediately before the strain, and, thus, is a measure of the maximum change in systolic blood pressure during the strain. Other criteria were also evaluated but this method best separated the normal subjects from those with ASD's. In the normal subjects, the range of the index was −13 to −85 with a mean value of −34. Thirteen of the patients with ASD's had indices above −12, the highest normal value, with a mean value for the group of +7. These patients all had pulmonic:systemic flow ratios of greater than 2.7:1. Three patients with small shunts had indices that fell within the normal range.

The Valsalva blood pressure response as measured by the Square Wave Index appears reliable in detecting left-to-right shunts in patients with ASD's when the pulmonary:systemic flow ratio is greater than 2.7:1. Since most patients with ASD's have shunt ratios exceeding this, this maneuver seems to be a useful screening test for the presence of such a defect.

Epicardio-Fibrous-Pericardectomy for Myocardial Revascularization: Clinical and Laboratory Evaluations

Thomas J. E. O'Neill and Gil E. Pablo, Philadelphia, Pennsylvania

Myocardial revascularization can be accomplished by a variety of methods, although wide variation in the extent of revascularizations is seen by objective laboratory studies. Objective data can be secured only by experiments that test the protective modalites created by each method. Operative survivals, premortem and postmortem radio-opacification studies, and micotissue studies, as well as longevity times, were used to evaluate each method in dogs whose coronary arteries had been gradually occluded with ameroid constrictors. In clinical cases, the only index of protection is the postoperative disappearance of angina and consequent loss of dependence on drugs.

Seventy dogs were operated upon: (1) Fifteen dogs were treated by control operation with ameroids and 4 appeared, by all modalities, to be protected. (2) Ten dogs were treated by Beck-I procedure, and 4 appeared similarly protected. (3) Ten dogs were treated with Thompson-Reisbeck operation, and 2 appeared similarly protected. (4) Ten dogs were treated by the modified Vineberg operation, and 7 appeared similarly protected. (5) Five dogs were treated by modified Knock operation, and 1 appeared similarly protected. (6) Five dogs were treated by arterialization of the coronary sinus by anastomosis with left inferior pulmonary vein, and 2 appeared similarly protected. (7) Fifteen dogs were treated with epicardio-fibrous-pericardectomy and 11 appeared similarly protected.

It was concluded that epicardio-fibrous-pericardectomy with interposition of ivalon sponge was the safest method that offered the maximum protection by providing an increase in homocoronary anastomosis, intercoronary anastomosis, extracardiac anastomosis, arterioluminal vessels, and the number of similar vessels communicating with the left ventricular lumen.

Currently 7 patients have been treated with this last procedure. Angina has disappeared in all, and the need for antispasmodics has been obviated.

Optimum Degree of Pulmonary Valvular Stenosis in the Presence of Insufficiency after Repair of the Tetralogy of Fallot

John J. Osborn and Frank Gerbode, San Francisco, California

In the anatomic repairs of tetralogy of Fallot, it is accepted that a severe residual pulmonary stenosis reduces right ventricular output. During a detailed review of 43 patients with tetralogy who underwent open-heart repair, it was found that, in patients in whom pulmonary valvular incompetence had been created, complete elimination of the pressure gradient across the pulmonary valve was also associated with low postoperative cardiac output and increased mortality.

It was then demonstrated by mechanical and mathematical analogue circuits that, in the presence of a competent tricuspid valve but an incompetent pulmonary valve, for any given strength of ventricular contraction, the cardiac output is minimal if there is no pulmonary stenosis, rises sharply as pulmonary stenosis is induced up to an optimal gradient across the pulmonary outflow tract, and then falls again as the optimal degree of stenosis is exceeded.

Pressure tracings from the right ventricle in patients with insufficiency, but no stenosis, show a slow systolic rise and a high diastolic pressure, the systolic pressure trace being triangular. If moderate pulmonary valvular stenosis is present, the right ventricular trace is more nearly normal and the early diastolic pressure within normal limits. It is evident that, in the absence of stenosis, the right ventricle fills rapidly and essentially completely by regurgitation from the pulmonary artery, whereas a partial outflow-tract stenosis prevents immediate refilling of the ventricle from the pulmonary artery and allows for a brief gradient in diastole between the pulmonary artery and ventricular pressures during which the ventricle can fill from the atrium.

These findings imply that, when it is necessary to induce pulmonary valvular incompetence in the course of surgery, a moderate residual degree of outflow tract stenosis is desirable to maintain right ventricular output.

Pulmonary and Cardiac Function Immediately after Intracardiac Surgery

John J. Osborn, Robert W. Popper, and Frank Gerbode, San Francisco, California

Thirty-eight patients with congenital heart disease were studied for up to 3 days after intracardiac repair under combined perfusion and hypothermia. Cardiac output and blood volume were determined by isotope injection and precordial counting. Arterial and venous pressures, usual vital signs, and blood drainage and replacement were recorded regularly. In addition, most or all of the following variables were measured; arterial pH, pCO_2 and standard bicarbonate, hematocrit, respiratory tidal flow, tidal volume, intrapleural pressure, and end-expiratory pCO_2. Lung elastic and nonelastic resistances were calculated when possible.

In general, patients with atrial septal defect, ventricular septal defect, aortic stenosis, and pulmonary stenosis showed an initial postoperative cardiac index of 4.5 to 6.5, representing an elevation over preoperative values of 2.5 to 4.5. Values 24 hours later did not vary more than 20 per cent, unless blood volume had changed appreciably.

However, in patients undergoing anatomic repair of the tetralogy of Fallot, the initial cardiac index ranged from 3.0 to 5.0 and was invariably lower by 24 per cent or more at 24 hours. This low output was often marked by low end-expiratory pCO_2, rapid rise in hematocrit, metabolic acidosis, and, later, by a marked increase in the gradient between end-expiratory and arterial pCO_2, suggesting ventilated but unperfused alveoli. Lung compliance and resistance measurements were usually normal. The most useful explanation of these findings is acute right-sided failure. In evaluating these patients, hematocrit or total patient-weight (common clinical guides for estimating effective circulating blood volume) were often entirely misleading. These patients did not have the usual ability to compensate for high or low blood volume. Therefore, accurate measurements of cardiac output, blood volume, and some aspects of lung mechanics were unusually important in medical management.

Long-Term Study of Serial Electrocardiograms in a Healthy Population

Robert Osborne, Boston, Massachusetts, William R. Harlan, Durham, North Carolina, and Ashton Graybiel, Pensacola, Florida

In spite of a large clinical experience with electrocardiograms, there is little information available on the physiologic changes in serial tracings in a normal population over a long period of observation. Serial electrocardiograms in a group of over 600 healthy men obtained in a continuing longitudinal study have been analyzed. Examinations and electrocardiograms were performed in 1939, 1952, and 1958; the mean age at initial evaluation was 21 years. Only minor changes were noted in the measured durations. The mean frontal QRS vector changed from an initial value of +60° to +40° over this 19-year period, and the mean T vector from +42° to +38°. Changes in the mean QRS vector were due largely to changes in the terminal forces which moved from +45° to +20°, while initial forces changed from +48° to +35°. Measurements have been made on the changes in Q-wave amplitude and duration in lead III over this period and have been related to vector changes. Correlations have been made with other physiologic variables, including blood pressure, weight, weight gain, blood lipids, and somatotyping. Serial observations on T-wave changes and variability and on S, S_2 S_3 pattern provide another viewpoint from which to interpret the importance of these findings. Definition of physiologic changes in electrocardiograms in this type of study affords a background from which pathologic alterations may be interpreted and their significance evaluated.

Demonstration of Extrathoracic Venous Obstruction Induced by Profound Negative-Pressure Breathing in Man

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It has been postulated that negative pressure breathing should lead to augmentation of right atrial filling and to increased cardiac output. Previous studies in these laboratories suggest that extrathoracic venous collapse occurs owing to the aspirating effect of lowered intrathoracic pressure during negative-pressure breathing at −20 cm. H_2O. This phenomenon may in fact impede venous return and has been observed by other investigators in animals. To demonstrate more clearly the extrathoracic venous obstruction induced by negative pressure breathing in man, 4 healthy male subjects in the supine position were studied before and at 10 minutes of full phase negative-pressure breathing at −40 cm. H_2O. The tip of one catheter was placed in the right atrium and another in a vein outside the superior thoracic inlet. Pressures were recorded from these catheters and from an indwelling arterial needle. Cardiac output was determined by central injection of I^{131}-labeled Iodopyracet and continuous serial arterial sampling. In all subjects at 10 minutes of negative-pressure breathing, right atrial pressure declined markedly during inspiration (−5.2 to −28.8 mm. Hg; S.D. = 6.5), while extrathoracic venous pressure increased (−8.6 to −4.9 mm. Hg; S.D. = 0.79). Breathing ambient pressure and respiratory variations of right atrial and extrathoracic venous pressures were identical (0.8 to 2.7 mm. Hg; S.D. = 0.87). This is interpreted as clear evidence of extrathoracic venous obstruction during negative-pressure breathing. The response of cardiac output varied. Mean arterial pressure was not altered by negative-pressure breathing; however, exaggerated variations in pulse are remarkably similar to those observed in pulsus paradoxus.

Comparative Effects of Local Anesthetics on Ventricular Conduction by Intracoronary Injection and Their Antagonism by Mephentermine Congeners

Marciano Panis, Zenaida Bagabaldo, Manila, Philippine Islands, Guido Ascanio, Frank Barrera, and Morton J. Oppenheimer, Philadelphia, Pennsylvania

Oxethazine, procaine, cocaine, lidocaine, and dibucaine hydrochlorides were injected into the left circumflex coronary arteries of anesthetized dogs with intact chests and without any obstruction of coronary flow at any time. Observations were made on 2 simultaneous standard or chest leads and on femoral blood pressure. Results were similar with each drug. These were: progressive lengthening P-R (increased conduction time through A-V node), and widening, slurring, and splitting of QRS (intramural increased conduction time), RST, and T-wave changes (injury current). Mephentermine and methoxy-mephentermine quickly reverses these. Dibucaine produces a dissociation between mechanical and electrical responses. It is the most toxic of the drugs studied, consistently producing ventricular fibrillation in doses one-tenth of that safely used for the other agents (1 mg. per Kg.).

Localization of the injection catheter was verified by acetylcholine and methylglucamine trizoate visualization by image intensifier.

Hemodynamic Alterations of Acute Pulmonary Thromboembolism (P)

Loren F. Parmley, Robert L. North, and Bruce S. Ott, San Francisco, California

Most studies of the pathophysiology of pulmonary embolization have utilized foreign materials or minute thrombi for embolization. To simulate pulmonary thromboembolism in man, preformed homologous thrombi made radiopaque and weighing 2.1 to 5.7 Gm. were introduced into the jugular and femoral veins of 10 dogs for a total of 27 embolic episodes (25 dogs with estimated 75 embolic episodes will complete this study). Systemic arterial blood pressure and pulmonary-artery and pulmonary-wedge pressures were continuously monitored. Regional cineangiograms were obtained prior to and immediately after each embolic episode. Cinefluoroscopic study at time of embolizations demonstrated fragmentation of the thrombus with progressive impaction of the emboli in the distal pulmonary arteries.

A rise in pulmonary-artery pressure to levels approximately twice the baseline without change in pulmonary-wedge pressure, but a slight to moderate fall in systemic arterial pressure characterized the transient changes of nonfatal embolization. Postembolic angiocardiograms revealed dilatation of the primary and secondary branches of the pulmonary arteries. Thus, reflex spasm of the small pulmonary arteries or arterioles is postulated. It was inferred from the normal wedge pressures that no alteration in pulmonary venous pressure occurred.

Prognosis could not be definitely correlated with the size of the embolus, number of previous embolic episodes, or degree of pulmonary hypertension; but a fall in systemic pressure to half the baseline value indicated a fatal outcome.

Death or recovery from pulmonary thromboembolism appeared to be an all-or-none phenomenon dependent upon reciprocal changes in pulmonary and systemic arteriolar resistance, with survival more directly related to the latter parameter.

Correlation of Clinical and Histologic Changes during the Course of Glomerulonephritis (P)

Alvin E. Parrish, Mary F. Watt, Vincent R. Pateras, E. Edward Bittar, and John S. Howe, Washington, D. C.

Fifty-two patients with acute glomerulonephritis whose ages ranged from 5 to 79 years have been studied by means of renal needle biopsy and various clinical tests, including determination of ASO titer, antikidney antibodies (AHK), and 24-hour urinary proteins. In 22 of these, serial kidney biopsies have been performed. Follow-up observations have been made from 1 month to 5 years from the onset of disease. Eight patients have developed the nephrotic syndrome, 3 of whom have died. Three additional patients have progressed to chronic glomerulonephritis, 1 of whom has died. Two patients have died during the acute phase of their disease and 1 other died of unrelated disease. Eight have persisted in having proteinuria, although other clinical signs of renal disease have vanished. Of the remaining patients clinical recovery has occurred (follow-up 2 months to 5 years) although histologic changes have persisted for as long as 3 years in those biopsied.

The histologic changes in the disease seem to go through fairly definite phases, which may be correlated with the clinical status of the patient. Persistently elevated serum titers of AHK antibodies indicate a poor prognosis.

Regulation of Physiologic Arteriovenous Communications in Man Demonstrated by Hydrocortisone Infusion

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An elucidation of the interrelation of hydrocortisone and arteriovenous shunts was sought through studies made in patients. The abnormal hemodynamic manifestations observed in patients with cirrhosis of the liver suggest that they are caused by multiple arteriovenous shunts in parallel. A relative increase in circulating steroids has been documented in cirrhosis, also.

Ten volunteer patients were studied at intervals of 2 to 30 minutes for 5 hours. Intravenous injections of hydrocortisone were given at intervals of 5 to 30 minutes for 4 hours. The maximal amount of hydrocortisone administered was 13 Gm. The Cr^{51} blood volume, venous and arterial oxygen saturation, systemic arterial blood pressure, venous pressure, and the heart rate were determined. Cardiac catheterization was performed in some patients.

In control patients not given hydrocortisone, stability of the parameters was observed. The subjects who received hydrocortisone showed significant increases in cardiac output, Cr^{51} blood-volume determinations, and venous oxygen saturation within 30 to 240 minutes. The magnitude of the responses was related to the quantity and frequency of hydrocortisone administration.

The decreased arteriovenous differences and the increased Cr^{51} blood volume and cardiac output make it appear that shunting of blood occurred in response to hydrocortisone. It is inferred that hydrocortisone exerted regulatory influences on physiologic arteriovenous shunts. Thus, it is believed that a cause-and-effect relation of steroids and arteriovenous shunts has been demonstrated. These data support the concept that varices and bleeding from the varices in patients with liver disease are secondary to functioning arteriovenous shunts.

Oxyhemoglobin Dissociation Curve and the Development of Acidosis during Profound Hypothermia (P)

Bruce C. Paton, Phillip B. Callaghan, Alexander Alexich, Takashi Tanaka, and Henry Swan, Denver, Colorado

A disc oxygenator was used to determine the simultaneous effects on the oxyhemoglobin dissociation curve of changes in pCO_2 and temperature. Curves for CO_2 tensions of 70, 60, 40, and 20 mm. Hg at 37, 30, 23, and 15 C. were constructed and demonstrated the opposing influences of depression of temperature and pCO_2 elevation.

The changes in the dissociation characteristics of oxyhemoglobin at 15 C. greatly inhibit the transfer of oxygen from the red cells to the tissues because of the minimal desaturation achieved at tissue oxygen tensions at these temperatures. At 15 C. with a pCO_2 of 40 mm. Hg only 7 per cent desaturation can occur between the arterial and venous blood. Hyperventilation to 20 mm. Hg pCO_2 would reduce this to zero. Small arteriovenous oxygen differences are, therefore, obligatory and are not necessarily related to tissue needs. The arteriovenous oxygen difference can be widened by increasing the pCO_2 of the blood. The importance of the oxygen available from solution in the plasma is obviously enhanced under these circumstances.

Pervascular cooling may result in tissues at 35 C. that have a high oxygen requirement when they are perfused by blood at 10 to 15 C. which is unable to release its oxygen. The arteriovenous oxygen difference may be only 1 to 2 volumes per cent, but the tissues are anoxic and resort to anaerobic metabolism. A metabolism acidosis results.

The adequacy and efficiency of oxygen exchange at low temperatures can be improved by having small temperature gradients between the blood and the tissues, high blood flows, and high arterial CO_2 tensions.

Thrombocytopenia in Cyanotic Congenital Heart Disease (P)

Milton H. Paul, Zinet Currimbhoy, Robert A. Miller, and Irving Schulman, Chicago, Illinois

The association of thrombocytopenia with cyanotic congenital heart disease has long been recognized, and it has been indicted as the cause of hemorrhage after thoracotomy for heart surgery.

In 200 children with cyanotic congenital heart disease, thrombocytopenia (platelet counts under 100,000 per cu. mm.) was extremely rare unless the hematocrit was greater than 65 per cent and/or the oxygen saturation was less than 70 per cent. Upon further analysis of this group, the influence of age became strikingly apparent. The incidence of thrombocytopenia in infants under the age of 1 year was only 10 per cent, whereas, in children more than 1 year it approached 60 per cent.

The individual influences of oxygen saturation and hematocrit upon the development of thrombocytopenia could not be determined with certainty. It was significant, however, that infants under the age of 1 year had a much higher incidence of extreme arterial oxygen unsaturation, yet they rarely had a hematocrit greater than 65 per cent. This might suggest either that arterial oxygen unsaturation must persist for a prolonged period, or that a hematocrit over 65 per cent must be concomitant for the development of thrombocytopenia.

Follow-up studies on operated children confirm the relationship between oxygen unsaturation, elevation of hematocrit, and the incidence of thrombocytopenia. When surgery was followed by an increase in oxygen saturation and by a decrease in hematocrit, there was a return of the platelet count toward normal levels.

Of considerable clinical importance was the observation that there was no correlation between the degree of operative hemorrhage (nonpump cardiac surgery) and the platelet count per se. Here, also, an influence of age was apparent, in that, with a similar degree of extreme thrombocytopenia, significant operative hemorrhage occurred only in patients over the age of 6 years.

Effect of Induced Anoxemia on the Ballistocardiogram

Raymond Penneys, Philadelphia, Pennsylvania

The ballistocardiogram (high-frequency, Starr type) was taken during the induced anoxemia test, with oximeter-control, to see if it would provide additional evidence of coronary insufficiency. The criterion for a "positive" test was an anginal attack or an abnormal electrocardiogram during induced anoxemia. Fourteen healthy, middle-aged subjects and 141 coronary suspects were studied. All healthy subjects had negative tests as did 94 of the suspects; 47 suspects had positive tests.

The ballistocardiogram of the healthy subjects was always normal on breathing air and remained so when low oxygen was administered. In the coronary suspects having a negative test, the ballistocardiogram on air was abnormal in 53 per cent of the cases and on low oxygen in 63 per cent; in those having a positive test, the comparable values were 75 per cent and 91 per cent. When the ballistocardiogram was abnormal on air, it became more abnormal in 30 per cent of the negative tests and in 58 per cent of the positive tests.

As in the case of the electrocardiogram, the usefulness of the ballistocardiogram in the detection of coronary insufficiency is further enhanced by its use during the induced anoxemia test.

Heart in Progressive Muscular Dystrophy

Joseph K. Perloff, Washington, D. C.

Twenty consecutive cases were studied by history, physical examination, radioscopy, electrocardiography, and phonocardiography. Criteria for selection were based solely upon the neurologist's diagnosis of muscular dystrophy of the pseudohypertrophic (17 cases) or the facioscapulohumeral type (3 cases). The former type were all males whose ages averaged 14 years and whose disease averaged 8 years' duration, with severity ranging from asymptomatic to incapacitated. The latter type were all females whose ages averaged 39 years and whose disease duration averaged 15 years' duration, with severity ranging from moderate to incapacitated. None had convincing cardiac symptoms when first seen. Nineteen remained asymptomatic. One, over a 3-year period, developed cardiomegaly, congestive failure, and complete heart block.

In the pseudohypertrophic group, heart disease was unequivocal in 6 (35 per cent), probable in 7 (41 per cent), questionable in 1 (6 per cent), and absent in 3 (18 per cent). In the facioscapulohumeral group, evidence was questionable in 1 patient and absent in 2.

Of the 13 pseudohypertrophic patients with evidence of cardiomyopathy, initial suspicion was the electrocardiogram in 12 and the x-ray (cardiomegaly) in 1. The most frequent and unique electrocardiographic alterations were peculiarly tall

V_1R waves without clinical evidence of right ventricular hypertrophy (53 per cent), and abnormally deep Q waves in Leads I, aV_L, V_{5-6} (24 per cent). An RS r′ in V_1 occurred in 24 per cent. Other findings included PR and QRS prolongation, left axis deviation, complete heart block, nodal extrasystoles, shifting pacemaker, and minor T-wave changes.

These results suggest that (1) *occult* dystrophic heart disease is commoner than generally emphasized, (2) the electrocardiogram is the most sensitive index of its presence, and (3) cardiac muscle may be involved chiefly in the pseudohypertrophic type.

Recognition of Strictly Posterior (Infra-atrial) Myocardial Infarction by Conventional Scalar Electrocardiography

Joseph K. Perloff, Washington, D. C.

Because strictly posterior infarction occurs without pathologic Q waves—and hence is generally missed—electrocardiographic evidence for its recognition was studied in 21 patients (3 autopsied). Criteria for selection were based on quantitative data (Pipberger) derived from orthogonal vectorcardiograms and electrocardiograms using Schmitt's corrected SVEC III leads. When these scalar and vectorial displays revealed abnormal anterior QRS shifts in the absence of right ventricular hypertrophy (R.V.H.), an electrically inert area in the posterior region of the left ventricle was diagnosed. Conventional electrocardiograms, supplemented by anterior and posterior chest exploring electrodes were then analyzed, with 100 normal controls.

The data indicate that strictly posterior infarction causes: (1) 0.04 second initial R waves in V_1 and in contiguous right anterior chest leads with, in the acute phase, S-T segment depressions and upright T waves; (2) a 0.04 second Q area posteriorly between the spine and left scapula; (3) rightward shift of the QRS transition zone in the "V" leads owing to loss of posteriorly directed QRS electrical forces; (4) slurring of the descending limb of the initial R in V_1 indicating abrupt change in QRS vector loop direction, and (5) no pathologic Q waves in any conventional leads unless contiguous lateral or diaphragmatic ventricular walls were infarcted. Exploring electrodes were of principal value in corroborating the diagnoses. V_1 R waves of 0.04 second were also found in (1) R.V.H.; (2) right bundle-branch block; (3) childhood age group; and (4) Wolff-Parkinson-White syndrome with an anteriorly directed delta vector. Attention to these differential diagnoses and to the foregoing electrical manifestations of strictly posterior infarction should facilitate its recognition by conventional electrocardiography.

Auscultatory and Phonocardiographic Manifestations of Pure Mitral Insufficiency (P)

Joseph K. Perloff and W. Proctor Harvey, Washington, D. C.

Acoustic manifestations of pure mitral insufficiency were studied in 22 patients. Fourteen were catheterized. Eight diagnoses were clinical (2 at autopsy).

The typical murmur was pansystolic, beginning with isometric systole, enveloping aortic valve closure, and radiating widely from apex to base, axilla, and back, from where vertebral bone conduction often caused downward progagation as far as the lumbar spine. It occasionally waxed in later systole (4 instances) probably because of increased turbulance as the left atrium received blood from both pulmonary veins and left ventricle. In 2 instances, the murmur consisted almost exclusively of this late systolic crescendo.

In 8 patients, unusual second-sound asynchrony occurred owing to premature aortic valve closure. In 4, the split widened with inspiration but never achieved expiratory synchrony. In the other 4, an inspiratory increase in right ventricular stroke time did not occur because the right ventricle had failed. P_2 therefore did not move, the widely split second sound remaining virtually fixed throughout respiration.

In 15 instances a third heart sound occurred because of rapid atrioventricular ("Y" descent) filling. In 3 patients this sound introduced a short diastolic rumble, and in 2 others it was preceded by an opening snap despite the absence of mitral gradients.

In 8 instances pressor amines were infused to increase regurgitation acutely by raising resistance to left ventricular contraction. The regurgitant murmur amplified markedly and the third heart sound became louder and earlier in diastole, reflecting an increased left atrial "V" wave and an increased rate of fall of the "Y" descent. Parallel studies with amyl nitrite inhalation had opposite effects.

Exit Block of Ectopic Pacemakers (P)

Alfred Pick and Richard Langendorf, Chicago, Illinois

Operation of a supraventricular or ventricular ectopic center, with a rapid or slow regular discharge, may be associated with a disturbance of propagation of impulses to the myocardium surrounding the pacemaker area. In the electrocardiogram the presence of such an "exit block" ob-

sures the true nature of a disturbance of rhythm, the recognition of which may have practical, clinical, and therapeutic implications. The types of block that can be demonstrated on the basis of a detailed analysis and the resulting arrhythmias, including bigeminy and other forms of group beating, correspond to those found in atrioventricular conduction disorders of second degree, viz., dropped beats that may or may not be preceded by a progressive conduction delay (the Wenckebach phenomenon). On occasion, the exit block can be shown to be unidirectional. How to recognize these types of block has been outlined for instances of: (a) slow and rapid parasystolic rhythms and (b) slow and rapid ectopic rhythms of nonparasystolic nature. Clinical aspects pertaining to mechanisms of Adams-Stokes seizures and to digitalis excess can be pointed out in some of the cases.

Anesthesia for Cardiopulmonary Bypass: A Community Hospital Experience

John A. Pierce, Leopold M. Trifari, Mario L. Garofalo, Pierino F. D'Elia, Norton A. Kazanjian, and Ulysses V. Golia, New Haven, Connecticut

The anesthetic experiences acquired in 60 consecutive cases of open-heart surgery employing cardiopulmonary bypass in a 370-bed community hospital are reviewed. Established anesthetic, pharmacologic, and physiologic principles have been strictly followed.

Individual management of each patient is stressed, avoiding standardization of anesthetic care. All patients are personally evaluated preoperatively by the anesthesiologist. Premedication usually consists of a barbiturate, merperidine, and promethazine according to the patient's age, weight, and estimated reflex excitability. Belladonna derivatives employed in our first 31 cases have been discontinued.

Anesthesia for adults is currently carried out with a sodium pentothal–succinylcholine chloride–nitrous oxide–halothane sequence. Children are often induced with cyclopropane and then maintained as adults.

With the onset of cardiopulmonary bypass, moderate generalized hypothermia is rapidly induced when indicated. Cardioplegia, if desired, is produced by the "saline slush" technic, which provides localized profound cardiac hypothermia.

Sixty consecutive cases of acquired and congenital heart disease have undergone surgery with an operative mortality of 10 per cent (6 cases) and a postoperative in-hospital mortality of 10 per cent (6 cases) resulting in an overall mortality of 20 per cent (12 cases). A previously unreported complication was the development of alopecia areata in 8 patients.

It is felt that these surgical procedures are possible at the community hospital level if a sincere effort is applied to the problem by all concerned. Experimentation should be left to those institutions where proper facilities exist. The prime purpose at the community-hospital level should be operative intervention carried out as expeditiously and safely as possible.

Problems Associated with the Practical Management of Long-Term Anticoagulant Therapy (P)

John W. Pollard, Michael J. Hamilton, Norman A. Christensen, and Richard W. P. Achor, Rochester, Minnesota

For evaluation of the difficulty of carrying out a satisfactory program of long-term anticoagulant therapy, a study was made of the records of 139 patients with vascular and thromboembolic diseases treated continuously with bishydroxycoumarin. The duration of treatment ranged from 3 to 69 months, averaging 18 months. The aim of treatment was to maintain the patient's prothrombin activity constantly within the "therapeutic range" (10 to 30 per cent of normal).

In only 57 per cent of cases was the prothrombin activity maintained within the therapeutic range as much as 80 per cent of the time. Forty-seven patients (34 per cent) had 61 bleeding episodes while receiving anticoagulant treatment. Of these episodes, 69 per cent occurred while the prothrombin activity was within the therapeutic range. Fourteen patients (10 per cent) had 15 hemorrhagic complications that threatened life or resulted in major disability; 3 of these 14 died. Hypertension was present in 30 per cent of the 47 patients who had bleeding and in 43 per cent of the 14 whose hemorrhagic complications were major, but in only 19 per cent of the entire group.

Seventy-eight patients discontinued anticoagulant therapy during the period of study and 64 of these were observed subsequently. Eleven (17 per cent) of the 64 had a vascular or thromboembolic episode within 2 months of stopping treatment; 3 of these patients died.

Long-term anticoagulant therapy presents practical problems that limit its usefulness and compel the physician to appraise carefully the indications for such treatment in each patient.

Arrhythmias after Closure of Atrial Septal Defects

Robert Popper, San Francisco, California, James Knott, London, England, Arthur Selzer, and Frank Gerbode, San Francisco, California

The records were reviewed of 127 consecutive patients who had closure of an inter-atrial septal defect of the secundum type with the aid of extracorporeal circulation between March 1957 and May 1961. There has been no mortality in the last 97 cases.

Of the entire series, 43 per cent had an arrhythmia some time after sugery. In patients under 18 years of age (76 cases) the incidence was 33 per cent, and there was no case of atrial fibrillation or flutter. In patients 18 to 55 years (51 cases), the incidence was 59 per cent; 7 of 8 patients over 45 years of age developed atrial fibrillation. Complete A-V dissociation occurs more frequently in the younger age group, spontaneously reverting to sinus rhythm in 9 out of 10 cases, though it may persist for as long as 9 days. Nodal rhythm was the most common arrhythmia, also reverting to sinus rhythm spontaneously.

In an effort to assess the role of atriotomy and open-heart surgery as a cause of these arrhythmias, analysis was made of a group of 28 consecutive patients who had their atrial septal defect closed by the "closed" external-suture technic. The incidence and type of arrhythmias tended to be the same.

Our series of 127 patients was also analyzed for length of perfusion, use of a patch, type of incision and cannulation, and presence of pulmonary hypertension (60 mm. Hg systolic or more). None of these factors appears to influence the incidence of arrhythmias.

It is concluded that older patients with interatrial septal defects have a higher incidence of postoperative arrhythmia. The increase in morbidity should be considered in determining the optimum age for surgery.

Comparative Study of Antibiotic Prophylaxis against Subacute Bacterial Endocarditis

Robert S. Pressman and I. B. Bender, Philadelphia, Pennsylvania

Transient bacteremias have been proved to follow various surgical procedures. Analyses of large series of patients with subacute bacterial endocarditis indicate that at least 50 per cent follow extraction of teeth. Forty-four patients were given oral and parenteral penicillin therapy (3,000,000 units) prior to the extraction of 2 or more teeth according to the 1957 and 1960 recommendations of the American Heart Association's Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis. Blood cultures taken immediately after extraction and 10 minutes after extraction were tabulated and compared with other series of patients. These were treated in the same manner after administration of parenteral penicillin in smaller doses, penicillin combined with streptomycin, or penicillin and streptomycin plus an oral antibiotic troche. The results of the present series indicate that increasing the penicillin dosage to a 3,000,000 unit level causes a significant reduction in the incidence of bacteremia. Analyses of series according to the levels of penicillin in the saliva and in the blood indicate that the effectiveness of the penicillin in suppressing the bacteremia varies according to the level obtained in these areas. The effectiveness of the penicillin is enhanced by the addition of streptomycin, and also by the local application of an antibiotic troche in the mouth one-half hour prior to the oral surgical procedure.

Thus protection against soiling of the blood stream requires a 2-fold type of antimicrobic prophylaxis: (1) at the site of the oral surgical procedure by means of antibiotic troches; (2) parenteral administration of suitable antibiotics, preferably bactericidal.

Coronary Heart Disease Among Physically Active and Sedentary Employees of the Railroad Industry

Thomas C. Puchner, Henry W. Blackburn, Henry L. Taylor, and Ancel Keys, Minneapolis, Minnesota

Railroad employees aged 40 through 59, including 846 sedentary clerks and 832 switchmen, were examined at 32 job sites of 12 operating railroads in the northwestern quarter of the United States. The examined group represented approximately 65 per cent of the men invited from a predetermined listing of employees to participate in this study.

A diagnostic classification system for epidemiologic studies in heart disease combining clinical and electrocardiographic criteria was employed. The age-adjusted prevalence rate for coronary heart disease (infarct plus angina) was 35 per 1000 for the combined group with rates of 24/1,000 for switchmen and 43/1,000 for sedentary clerks ($p = 0.03$). The age-adjusted prevalence rate for myocardial infarction alone was 26 per 1,000 for the combined groups with rates of 21/1,000 for switchmen and 29/1,000 for clerks.

Medical records of the railroads provided adequate disease information on about one-third of the nonrespondents (366 men), as well as comparable data on 645 of the men examined. Analysis of these data showed a frequency of 19 coronary cases per 1,000 for respondents and 14 per 1,000 for nonrespondents. These data suggest that the overall prevalence rate is not biased by coronary-disease concentration among either the nonrespondents or the respondents. However, it is not known whether differential concentration occurred in the occupational groups.

More secure conclusions about the relationship between the habitual physical activity of their occupational class and the frequency of coronary heart disease must await the long-term follow-up which is planned for these men.

Renal, Pulmonary, and Systemic Circulation in Patients with Left-to-Right Cardiac Shunts

Robert L. Rainey,† James W. Culbertson, and G. Daniel Copeland, Memphis, Tennessee

Renal circulation in patients with "arteriovenous" cardiac shunts appears not to have been investigated previously. We have studied 11 patients: 4 women and 3 men with atrial septal defect, 2 women and 1 man with ventricular septal defect, and 1 woman with a coronary artery–right atrial communication. Standard renal clearance methods (Smith) with inulin for glomerular filtration rate (GFR) and sodium para-aminohippurate for effective renal plasma flow (ERPF) were employed for observing renal circulation, and both direct and indirect (Fick-Cournand) methods for studying pulmonary and general systemic hemodynamics. Patients were studied supine in the preoperative, fasting, resting state. None had clinical evidence of myocardial decompensation.

GFR averaged 116 ml./min./1.73 M.^{2} (range 86 to 176) in women and 117 (range 93 to 153) in men, and usually was normal. Contrariwise, ERPF averaged 428 ml./min./1.73 M.^{2} (range 307 to 625) in women and 467 (range 379 to 628) in men and usually was sharply reduced. Resultant filtration fractions invariably were elevated, often strikingly, averaging 0.28 (range 0.23 to 0.34) in women and 0.26 (range 0.24 to 0.29) in men. Systemic blood flow (average 5.3 L./min./1.73 M.^{2}) failed to show a reduction comparable to the relative renal ischemia. Increased average pulmonary circulation (10.6 L./min./1.73 M.^{2}) reflected the left-to-right shunting. No important pressure aberration was found in right atrium or ventricle, pulmonary artery or wedge position.

This renal hemodynamic abnormality demonstrates again the autonomy of renal circulatory control. Perhaps it ensures adequate glomerular filtration despite a contracted systemic arterial blood volume.

Elastic Properties of the Right-Ventricular Myocardium in Children with Right-Ventricular Hypertension (P)

William J. Rashkind, Philadelphia, Pennsylvania

The end-diastolic volume of the right ventricle (EDV), the end-systolic volume of the right ventricle (ESV), the stroke volume of the right ventricle (SV), and the fraction of the EDV ejected as SV (f) were measured in 14 patients with acyanotic congenital heart disease. The technic used was a modification of that described by Holt. The conductivity cell of Holt was replaced by a small, sensitive, recording thermocouple, and the injectate was isotonic saline solution at 0 C. From these data, assuming the right-ventricular cavity to be spherical, it is possible to calculate the dimensions of the sphere. By comparing the dimensions at the end of systole with the peak right-ventricular pressure, a force-length relationship can be derived. From these data a figure equivalent to Young's modulus of elasticity can be calculated for the right-ventricular myocardium.

Six patients with normal right-ventricular pressures had these values: mean EDV, 142 ml./M.^{2} (73 to 290); mean ESV, 90 ml./M.^{2} (51 to 226); SV, 52 ml./M.^{2} (26 to 57); mean f, 32 per cent (19 to 47); and elastic modulus, 0.09. Five patients with right-ventricular systolic pressures from 45 to 55 mm. Hg measured: mean EDV, 122 ml./M.^{2} (84 to 167); mean ESV, 81 ml./M.^{2} (42 to 125); mean SV, 41 ml./M.^{2} (33 to 70); mean f, 36 per cent (25 to 50); and elastic modulus, 2.7. Three patients with right-ventricular pressures equal to, or greater than, systemic levels (70 to 120 mm. Hg) had: mean EDV, 252 ml./M.^{2} (90 to 405); mean ESV, 215 ml./M.^{2} (60 to 355); mean SV, 37 ml./M.^{2} (30 to 50); mean f, 25 per cent (13 to 32); and elastic modulus, 0.46.

The data suggest that right-ventricular stroke volume is maintained as outflow resistance increases, even though f decreases. This is accomplished by ventricular dilatation resulting in an increase in EDV. With moderate elevations in the right-ventricular pressure, there is a moderate increase in EDV and a marked increase in elasticity. When right-ventricular hypertension is severe, there is a marked increase in the EDV and a fall in elasticity.

Prolonged Extracorporeal Oxygenation in Apneic Dogs with a Pumpless Oxygenator

William J. Rashkind, Alfred Freeman, and Dorothy Klein, Philadelphia, Pennsylvania

To provide extracorporeal oxygenation, various combinations of artificial oxygenators and artificial pumps have been employed. In the many situations in which the heart could be used as the pump, an oxygenator need be the sole external device employed. In these experiments, a simple, all plastic, bubble-type oxygenator was interposed between a femoral artery and femoral vein. Arterial pressure, pulse rate, and arterial oxygen saturation were monitored continuously. Total and plasma hemoglobin levels, pO_2, and pH were meas-

ured at frequent intervals. With the oxygenator in place, but closed, pulmonary capillary alveolar block was produced in dogs to a degree sufficient to decrease the arterial oxygen saturation to 5 to 20 per cent, and to maintain it at these low levels even during positive-pressure ventilation of the animals' own lungs with 100 per cent oxygen. The oxygenator was opened and the arterial oxygen saturation increased to 60 to 70 per cent with a blood flow through the oxygenator of 35 to 50 ml./Kg. When the oxygenator was closed, the arterial oxygen saturation returned to the prior low levels (5 to 20 per cent). Apneic animals were maintained on the oxygenator for as long as 6 hours without hemolysis or acidosis, with stable pulse rates and arterial pressures, and at arterial oxygen levels of 60 to 80 per cent saturation.

Evaluation of Function of Hearts Removed After Death, Using the Isolated Perfusion Technic (P)

S. Frank Redo and Frank Glenn, New York, New York

Successful transplantation of homologous hearts will depend upon 3 factors: (1) solution of immunologic problems; (2) development of technics for acquisition and storage of hearts; and (3) heart function after postmortem removal. This investigation concerns the third factor.

Guinea pigs weighing 500 to 600 Gm. were killed by a blow on the head. The hearts were removed and perfused with Ringer-Locke solution. Four groups of hearts were studied: those removed immediately, and those removed 15, 30, and 60 minutes after death. These were compared with 8 control hearts removed antemortem. Amplitude of contraction, electrocardiogram, and time to failure were recorded. The amplitude of contraction of hearts removed immediately after death was equal to that of control hearts. Those removed 15 minutes post mortem had 95 to 100 per cent of control amplitude. Hearts perfused 30 minutes after death had only 35 to 50 per cent of control amplitude. No mechanical activity could be measured in hearts removed 60 minutes after death. Electrocardiograms were unremarkable in hearts removed up to 30 minutes post mortem. Those studied 60 minutes after death revealed low voltages and, occasionally, fibrillation. The longer the interval between death and perfusion, the sooner failure occurred.

The results indicate that guinea-pig hearts must be removed within 15 minutes post mortem in order to be effective homologous transplants. Although species differences undoubtedly exist, the results suggest that there is a definite, probably short, period of time after death when a heart can be removed and still function.

Simultaneous Determination of Volumes of Both Ventricles in the Intact Dog (P)

Tim D. Reedy, Dallas, Texas

The highly irregular shape of the right ventricle makes direct determination of its volume from biplane cinefluorographic films impossible; left ventricular (LV) volume, on the other hand, can be determined from such films reasonably satisfactorily. A method, utilizing the additional fact that the combined internal volume of both ventricles can be determined, has been evolved. In practice, it is possible to trace the outlines of the LV cavity in such a way that septal volume is included. Thus, total ventricular cavitary volume (T), minus volume of left ventricular cavity (L), and of interventricular septum (S), yields volume of right ventricular cavity (R), or: $R = T - (L + S)$.

The method has been applied to 10 intact, anesthetized dogs. Injection of contrast medium is in 2 stages; the first injection, into the right atrium, precedes the second by 4 seconds. Cameras are started simultaneously with the second injection when both ventricles are opacified. Filming is at 30 frames/second. Tracings of both ventricular cavities together, and of LV cavity with septum, are then made from 35-mm. negatives (3 to 5 cardiac cycles) and volumes are determined in absolute values by a scanner-computer.

Peak volumes of right ventricle and left ventricle varied between 50 and 80 ml. Volumes of interventricular septa are sometimes as high as 20 ml., but do not remain completely constant owing to geometric artefacts. For the first time, the method renders simultaneous ventricular-volume curves approachable; they parallel each other reasonably well, but appear to deviate owing to the influence of respiration and other factors.

Studies of Coronary Artery Distribution in Congenitally Malformed Hearts (P)

Keith Reemtsma, Charles G. Longenecker, and Oscar Creech, Jr., New Orleans, Louisiana

Studies of coronary artery distribution were performed in 162 hearts with congenital malformations and in 24 normal hearts. Technics of study included injection of barium-latex or lead-vinylite suspensions in fresh specimens, with roentgenograms and photographs before and after clearing. Gross dissection was performed on formalin-fixed specimens.

Anomalous distribution of coronary arteries occurred most commonly in specimens with transposition complexes and in tetralogy of Fallot with marked dextroposition of the aorta. In tetralogy of Fallot, the 2 most common variants were: (a) anomalous anterior descending artery arising from

the right coronary artery; and (b) single right coronary artery with the left coronary branch passing across the right ventricular outflow tract. These anomalies are of considerable surgical significance, as the usual type of ventriculotomy for open repair of tetralogy would result in division of a major coronary artery. The most frequent pattern of coronary artery distribution in transposition of the great vessels involved reversal of the coronary arteries. In 14 of 18 specimens, the left coronary artery arose from the left anterior sinus and the right coronary artery from the posterior sinus.

The artery to the atrioventricular node and bundle rose consistently in the region of the coronary sinus, usually from the right coronary artery. In ostium primum defects, this vessel lay in a vulnerable position beneath the inferior rim of the defect. In atrial defects of the secundum type and in ventricular septal defects, this vessel lay a safe distance from the area of repair.

Hormonal Regulation of Myocardial Metabolism and Contractility: Glucagon and Epinephrine (P)

Timothy J. Regan, Patrick H. Lehan, Dorothy H. Henneman, Alberto Behar, and Harper K. Hellems, Jersey City, New Jersey

The hyperglycemic glycogenolytic factor of the pancreas appears to share certain metabolic properties with epinephrine. Since the cardiac effects of purified glucagon have not been described in the intact animal, 7 anesthetized dogs were given 50 μg. of purified glucagon into the left coronary artery to minimize systemic metabolic influence. The duration and maximum rate of left-ventricular isometric pressure rise were used as indices of contractile response. Within 10 seconds, an increase in left-ventricular contractility occurred, a maximal increment of 80 per cent occurring by 2 minutes without altered ventricular pressures. A transient nodal tachycardia at 30 seconds was followed by a sinus tachycardia, and both inotropic and chronotropic responses persisted 30 minutes. The myocardial metabolic response, followed sequentially by arteriovenous differences, included diminished carbohydrate uptake and metabolism, reduced oxygen extraction, increased coronary flow, myocardial oxygen consumption, and potassium uptake.

Intracoronary infusion of a molar equivalent of synthetic *l*-epinephrine (10 μg.) induced a rapid but more modest (20 per cent) increase in contractility followed by a small rate increment. The changes in carbohydrate metabolism, oxygen extraction, and potassium uptake paralleled those of glucagon, suggesting that this hormone's effects are sympathetic mediated.

Reserpine depletion of myocardial norepinephrine stores in 4 experiments did not interfere with the hemodynamic or myocardial metabolic response to glucagon. Additionally, the lack of systemic pressor change would exclude this amine as relevant to the mode of action. The rapidity of onset of the initial contractile response would not favor adrenal medullary epinephrine as the mediator, but requires a myocardial source of this or a related amine, unless glucagon itself has a primary effect on the heart, acting on metabolic pathways related to those of epinephrine.

Hemodynamic Study of Thrills and Murmurs in Pectus Excavatum (P)

Clifford S. Reusch, Tokyo, Japan, and Bertram J. Allenstein, Beverly Hills, California

Published hemodynamic data in pectus excavatum are limited to 42 cases. We present the hemodynamic data of 8 patients with pectus excavatum, referred because of auscultatory findings which were thought to be indicative of organic heart disease: 3 mitral insufficiencies, 2 interventricular septal defects, 2 interatrial septal defects, and 1 either interatrial or interventricular septal defect.

All patients had 14-lead electrocardiograms; direct spatial vectorcardiograms utilizing Kimura, Grishman, and Frank systems; phonocardiograms; cardiac fluoroscopic and x-ray examination; and cardiac catheterization. Two patients presented with incomplete right bundle-branch block; 3 presented with precordial leads consistent with the diagnosis of right-ventricular hypertrophy. However, direct spatial vectorcardiograms were within normal limits in all cases. Phonocardiograms demonstrated prominent systolic murmurs and persistent splitting of second sound at the pulmonic area. In 6 patients, a thrill was palpable. Cardiac fluoroscopy and x-ray revealed prominent pulmonary-artery segments in all patients, but the rest of the pulmonary vasculature and the heart size were within normal limits.

Cardiac catheterization, including dye-dilution studies, revealed normal oxygen saturations, systemic and pulmonary-vascular resistance, and response to exercise. In 1 patient, resting cardiac output was elevated, and in 2 cases there were 5-mm. and 9-mm. gradients across the pulmonic valve. Angiocardiograms were normal in the 2 cases done.

Our findings of a benign thrill had not been mentioned previously among the peculiarities of pectus excavatum. The electrocardiographic abnormalities and prominent pulmonary-artery segments

are believed to be due to the heart position within a deformed chest.

Normal Right-Heart Pressures Following Pericardiectomy for Constrictive Pericarditis

David W. Richardson, Lewis H. Bosher, Donald P. Fitzpatrick, and Eugene M. Wyso, Richmond, Virginia

Earlier investigators of the response to pericardiectomy in chronic constrictive pericarditis demonstrated marked clinical improvement, but continuing abnormality of right-ventricular and right-atrial pressures, similar to the typical patterns seen preoperatively. In a series of 11 consecutive patients subjected to extensive pericardiectomy between 1957 and 1960, postoperative cardiac catheterization done in 7 subjects showed normal right-heart pressures in 6. The seventh had typical "M"-shaped atrial pressure and high right-ventricular–end-diastolic pressure 2 weeks after pericardiectomy. He died in an alcoholic debauch 5 months later, before catheterization could be repeated; at autopsy his heart appeared normal. Three other patients each demonstrated slow clinical recovery and had caseous necrosis and acid-fast bacilli in pericardial sections. Catheterization 2 and 7 months after operation in 2 of these showed continued elevation of end-diastolic ventricular and "W"-shaped atrial pressures. Repeat study 5 months and 5 years later in these 2 patients showed perfectly normal pressures. Catheterization 7 years after operation showed normal pressures in the third of these patients with delayed recovery. Comparison with earlier series suggests that extensive pericardiectomy probably accounts for the normality of right-heart pressures eventually demonstrated in our patients. The small series prevents definite conclusions, but suggests that active tuberculosis may be associated with delayed clinical and physiologic recovery.

Influence of Pulmonary Vascular Maturity on Response to Subclavian Pulmonary Arterial Anastomosis (P)

John W. Richardson, Clay E. Phillips, Jr., James A. DeWeese, James A. Manning, and Earle B. Mahoney, Rochester, New York

The pathogenesis of the vascular changes of pulmonary hypertension has been studied experimentally, usually by the creation of systemic to pulmonary-arterial shunts in adult dogs. No previous study has been reported on the comparative responses of a mature and an immature pulmonary vasculature to experimentally induced pulmonary hypertension.

End-to-end left-subclavian to left-pulmonary-arterial anastomoses were successfully performed on 43 puppies, 3 to 11 weeks old. Lung biopsies and pressure studies were taken at time of shunt and from 1 hour to 14 weeks later. Histologic changes in the pulmonary vasculature were assessed by determining the lumen to wall (L/W) ratio in small muscular arteries and proximal arterioles 50 to 200 μ in diameter.

Twenty-two of the 26 puppies with a more immature pulmonary vasculature at shunt (L/W ratio less than 5.9) showed arteries with thinner walls and larger lumens at biopsy. Sixteen of the 17 puppies with a more mature vasculature at shunt (L/W ratio greater than 5.9) showed arteries with thicker walls and smaller lumens at biopsy. The left-pulmonary arterial pressure was significantly and equally elevated in both groups. The changes occurred without relation to duration of the shunt.

Puppies with an immature pulmonary vascular bed do not develop vascular changes of pulmonary hypertension when subjected to an elevated pulmonary-arterial pressure. This suggests that factors in addition to an elevated pulmonary-arterial pressure must cause the development of the vascular changes of pulmonary hypertension seen to be clinically associated with congenital heart malformations.

Percutaneous Coronary Arteriography

Howard J. Ricketts and Herbert L. Abrams, Palo Alto, California

A number of percutaneous technics have been studied in an attempt to define a dependable, safe, and simple method of coronary arteriography. Variations in technic have included the following: (1) use of different catheters, such as a straight catheter with an end opening, a straight catheter with a closed end and side openings, a straight catheter with end opening and side openings, a loop catheter with end opening and side openings, and catheters selectively shaped for the right and the left coronary arteries; (2) application of rapid filming using conventional biplane Elema roll-filming, single-plane 5-inch and 9-inch image intensified cine, and biplane cineangiocardiographic studies; (3) use of various media, in differing concentrations and volumes; and (4) application of varying degrees of increased intrathoracic pressure.

Among the methods studied, the loop catheter has seemed most useful for application to clinical subjects, and recording either with large-film technics or with cine has proved quite satisfactory. In addition, a simple percutaneous transfemoral selective coronary arteriographic technic has been

developed and studied intensively at the animal level. Such a technic can only be coupled with cine recording.

Electronic System for Electrocardiographic Analysis

Arthur E. Rikli, Cesar A. Caceres, Sidney Abraham, Washington, District of Columbia, Walter E. Tolles, and Charles A. Steinberg, Deer Park, New York

A pilot study has demonstrated the feasibility of automatic analysis of electrocardiograms by a properly programmed computer. The system is capable of processing an electrocardiographic lead, without human intervention, to provide amplitude and duration values of the P, P-R, Q, R, S, S-T, T, Q-T, U, and R-R. Any other desired variable in the electrocardiogram may also be located and arrhythmias may be detected. The measurements can be used for further analysis by computer-statistical methods and may thus be of value in standardization of electrocardiographic data from epidemiologic studies. Similarly, using measured values of electrocardiographic waves from a single standard lead and statistical equations programmed for a computer, it has been shown to be feasible to distinguish clinically identifiable normal and non-normal electrocardiograms. The electrocardiographic measurements may also be programmed for comparison with "standard values" of electrocardiograms, or according to the interpretative logic or criteria designated by the physician to serve him as an aid in his diagnosis.

Simple Connection of Gut Arteries or Veins by Implantation in the Lumen: Of Possible Value in Massive Disasters

Joseph T. Roberts, Buffalo, New York

In massive disasters, where facilities for connecting blood vessels by usual technics have become exhausted, salvage of limbs and lives can be increased by placing the proximal cut artery's end into the lumen of the distal artery or into the side of an adjacent vein, according to successful anastomoses in over 338 experiments on animals. The 2 vessels can be anchored with perfect control of bleeding by usually only 1 suture, which may be of any available threadlike material. Only 1 knot is required and this is outside of contact with the luminal stream of blood. Clotting at the connection is not more frequent than with comparable studies using Carrel's intimal sutures, cannulas with lining using vascular segments, or using anastomosis over a guide structure. The advantage is very great as far as cost and availability are concerned, as well as having greater speed. The stapling devices available in some areas have comparably enormous disadvantages of being very expensive, seldom available, and extremely intricate, so as to require highly specialized training of personnel and much time for loading. Flow through these vessels after intraluminal-implantation anastomosis has been adequate or normal, according to inspection, injections with colored dyes or plastic corrosions, and measurements of pressures or flow above and below the site. Carotid, femoral, jugular, coronary, pulmonary, subclavian, aortic, and other vessels, as well as Teflon sleeves, have been so anastomosed. A plastic prosthesis between widely separated aortic ends has been so implanted successfully also.

Autoregulation, Critical Closing Pressure, and Vascular Resistance: Passive Functions of Collapsible Vessels

Simon Rodbard and Kizuku Kuramoto, Buffalo, New York

Autoregulation, critical closing pressure, and some phases of vascular resistance can be accounted for on the basis of the hydrodynamics of flow through passive collapsible vessels: arteries, veins, or rubber tubing. Thus, flow is uniform despite large changes in pressure head in a system in which "arterial" pressure head communicates directly with extravascular (tissue) compartment. Other experiments have demonstrated that delivery rate remains unchanged as long as "tissue" pressure exceeds venous (outlet) pressure, regardless of venous-pressure level; elevation of venous pressure distends the collapsed vessel and reduces resistance even though the arteriovenous pressure gradient is reduced. "Autoregulation" can, therefore, occur in passive vessels. "Static" or "critical closing" pressure also depends on the balance between intra- and extravascular (transvascular) pressures. As long as transvascular pressure is positive, vessels are distended and resistance to flow is minimal. When transvascular pressure is negative, the vessel collapses and resistance increases markedly. This passive effect accounts for "critical closing," obviating the need to invoke surface forces or muscular tone. These examples, based on a wide variety of experiments on flow through collapsible vessels, indicate that peripheral vascular resistance and control of specific vascular beds may be determined, in significant part, by transvascular pressure and the collapsibility of the capillary in some organs, such as the lung. Important roles for capillary permeability, degree of solation of the pericapillary tissues, and for venomotor tone in the regulation of transvascular pressure, collapsibility, and therefore in local vascular resistance, are indicated.

Myocardial Power

Simon Rodbard, Christine B. Williams, Buffalo, New York, and Eric Berglund, Göteborg, Sweden

Analysis of data on coronary oxygen uptake (qO_2), cardiac frequency (F), stroke output (V), and mean arterial pressure (P) has led to a new approach to myocardial energetics. By considering the stroke output to be spheroid, intraventricular radius is calculated as proportional to $V^{1/3}$. The product of radius and mean arterial pressure ($PV^{1/3}$) is the peak tension of a given beat. Oxygen uptake per unit of tension increases with heart weight (W), and with frequency (F), so that

$$qO_2 = a \cdot FPV^{1/3} \cdot W + bW,$$

in which a and b are constants. The basal oxygen cost of noncontractile myocardial functions (bW) is obtained by extrapolation. Heart weight reflects the surface area (r_o^2) of an unstressed spheroid shell of myocardium. Tension/beat ($PV^{1/3}$) is proportional to the number of shells of myofibrils activated in that beat. Thus, qO_2, expressed as power (erg/min.), can be correlated dimensionally and quantitatively with the power developed by the heart, $PV^{1/3}\ r_o^2$, also in erg/min. Myocardial power per beat varies widely, depending on the number of shells mobilized, and is therefore not all-or-none. Net myocardial efficiency (E_n) increases with stroke volume according to the relationship $E_n = V^{2/3}/_{aW}$. The analysis demonstrates that end-diastolic ventricular pressures and volumes have no direct effect on myocardial energetics. The apparent relationships with oxygen uptake, arterial-pressure level, stroke output, work, etc., result only because the volume in the heart during systole determines the rate of mobilization of tension and the peak tension achieved during systole. The results favor restatement of the "Law of the Heart" entirely in systolic rather than diastolic terms.

Effect of Change of Posture on Added Heart Sounds

Philip Rodin and Bernard Tabatznik, Baltimore, Maryland

The value of change of posture in discriminating between the various added heart sounds has not been generally recognized. Moreover, the influence of heart failure on the results has received little attention. These points have been studied in various groups of patients.

Auscultation and spectral phonocardiography showed that even loud atrial sounds disappeared on standing in 10 of 14 patients. They sometimes reappeared after standing exercise. The remaining 4, all left atrial, moved toward the first sound, in 1 becoming an "atrial component." In the sitting patient, even with his legs dependent, the sound was usually still obvious.

In standing subjects, physiologic third sounds disappeared, but third sounds in left ventricular failure persisted. In 2, re-recorded after failure was well controlled, the third sound occurred later and then disappeared on standing.

Quadruple rhythm persisted on standing in 5 of 16 patients and the atrial sound alone in 2. The atrial sound often migrated toward the first, and sometimes the third sound was delayed. Those in whom both sounds persisted all had grossly diseased hearts.

The aforementioned effects were usually accompanied only by trivial changes in blood pressure. Pulmonary and aortic ejection clicks persisted on standing; opening snaps were unaffected or delayed.

This study indirectly confirms the importance of venous return in the production and timing of diastolic gallop sounds. Postural alterations in these sounds may help in difficult cases to distinguish atrial from ejection sounds and serve as useful guides to the patient's clinical state.

Specificity and Sensitivity of Electrocardiographic Voltage Criteria in Early Left Ventricular Hypertrophy

Manuel Rodstein and Richard S. Gubner, New York, New York

Voltage criteria of left ventricular hypertrophy established by correlations with autopsy findings or in persons with advanced hypertensive heart disease are not well suited for detection of early left ventricular hypertrophy, since myocardial disease and advanced age both may reduce the QRS voltage, notably in limb leads.

A study was carried out of 234 male insurance applicants (average age 45) who exhibited one or more of the numerous voltage criteria recommended in limb, augmented unipolar limb, and precordial leads. The cases were grouped into: (a) those who were clinically normal and in whom voltage abnormalities were ostensibly falsely positive (70); (b) those with presumptive or early left ventricular hypertrophy (hypertension or increased cardiac transverse diameter, 11 to 15 per cent above predicted) (130); and (c) those with definite clinical hypertrophy (34 cases).

The highest coefficient of specificity (82 per cent) was found for the criterion $R1 > 15$ mm. (1.5 mv.). Inferior specificity was shown by the criterion $Rv5 - 6 + Sv1 > 35$ mm. (3.5 mv.), with 35 false positives among 126 cases with this finding. The highest coefficient of sensitivity among the various individual criteria was provided by

the sum Rv5 – 6 + Sv1 > 35, which was positive in 91 of the 164 cases with presumptive or definite hypertrophy.

Highest utility coefficient (specificity times sensitivity) (59 per cent) was obtained when either of 2 criteria was present, i.e., R1 > 15 or Rv5 – 6 + Sv1 > 35. Utility of these was greater in the presence of left-axis deviation (65 per cent) than in its absence (51 per cent). Other voltage criteria which have been proposed either individually or in combination were inferior as to specificity, sensitivity, and utility.

Effects of Hemorrhage on Precordial Pulsatory Motions

Leslie M. Rosa,† Donald M. MacCanon, Toshihiko Inoue, and Elie Y. Sadik, Chicago, Illinois

Precordial acceleration tracings were recorded during protracted hemorrhage in 10 dogs. Changes were correlated with electrocardiogram, external and intracardiac phonocardiograms, and intracardiac pressures. The initial blood loss, with decreased left-ventricular pressure, caused a 25 to 50 per cent reduction in the early systolic amplitude of the precordial acceleration tracing. Continued hemorrhage resulted in a decrease in the amplitude of the mid-systolic deflection. At preshock levels, amplitude changes were observed during reduced ejection. Loss of vascular tone (shock) was associated with an abrupt change in acceleration pattern and large deflections. This stage was characterized by dissociation between electrical and mechanical systoles, disappearance of the second heart sound, and also abnormal acceleration pattern in diastole. The gradual extension of the pulsatory abnormalities from early systole to subsequent phases of the cardiac cycle was related to anemia and hypoxia (electrocardiographic changes), and is in accordance with clinical observations in ischemic heart disease. The magnitude of precordial pulsatory forces seems directly related to total blood volume (myocardial blood supply?) and probably inversely related to peripheral resistance. A consistent relationship to levels of ventricular pressures could not be clearly demonstrated.

Objective Study of Therapeutic Effect of Triparanol and Warfarin in Peripheral Vascular Disease

Leonard B. Rose, Portland, Oregon

Objective evaluation of 16 patients with established peripheral vascular disease due to atherosclerosis was initiated 3 years ago. The objective method used was plethysmography, both digital and segmental, according to the technic of Travis Winsor, done serially at 6- to 9-month intervals. Vasodilating procedures (posterior tibial nerve block, reflex heat, and/or ethanol ingestion) were used to obtain maximum digital blood flow.

All 16 patients received 250 mg. of triparanol daily for periods ranging from 6 to 13 months. Ten patients served as their own controls, having been tested serially for the 12 to 24 months prior to triparanol therapy. Nine patients had been maintained on warfarin therapy from the time of initial observation. All patients had serial cholesterol studies and were seen regularly.

The results indicate that 12 of the 16 patients showed increased amplitude of the digital and segmental plethysmogram at the time of the last vasographic study during the administration of triparanol. Two patients had slightly diminished readings and 2 patients were unchanged.

Although this study was undertaken to evaluate the results of long-term medical management of occlusive peripheral atherosclerotic disease with the use of a cholesterol-depressant agent, further analysis of our data revealed the interesting fact that all 9 patients receiving anticoagulant therapy showed consistent improvement on objective testing, whereas only 3 of the 7 patients not receiving warfarin showed such improvement.

Sympathoadrenal Response and Serotonin Release During Hemorrhagic Shock in Epinephrine- and Endotoxin-Tolerant Dogs

J. C. Rosenberg, Minneapolis, Minnesota

The pattern of response of the sympathoadrenal system in hemorrhagic shock has been characterized and compared with the response which is seen following the administration of endotoxin. Similarly, the degree of serotonin release in endotoxin shock has been measured and compared with the minimal response demonstrated by animals subjected to hemorrhagic shock. The above studies were conducted on a total of 19 dogs that had serial determinations of blood volume, hematocrit, platelets, blood pressure, serum-serotonin concentration, and plasma-epinephrine and norepinephrine concentration. In order to clarify the mechanism whereby animals which have been rendered tolerant to otherwise lethal doses of epinephrine or endotoxin have a greater resistance to irreversible hemorrhagic shock than untreated animals, 4 epinephrine-tolerant and 5 endotoxin-tolerant dogs were subjected to hemorrhagic shock. The same parameters were measured. The peripheral circulating catecholamines and serum-serotonin concentration in dogs rendered tolerant to epinephrine or endotoxin and then subjected to hemorrhagic shock did not differ significantly from untreated animals. It is thus concluded that the protective mechanism resides in the cardiovascular

response to sympathoadrenal activity rather than an alteration in the sympathoadrenal response to hemorrhagic hypotension per se.

Identification of Kidney Antibody in Nephritis and Nephrosis

J. Loren Rosenberg and Herbert O. Sieker, Durham, North Carolina

The role of immune mechanisms in nephritis and nephrosis is well recognized, and the identification of kidney antibody in these illnesses has been reported in the past. It was the purpose of this study to use a modification of the tanned red cell technic and the globulin fraction of serum to identify kidney antibody. Observations were made on sera from normal controls and from 8 patients: 4 with nephrotic syndrome, 2 with acute nephritis, and 2 with lipoid nephrosis. The antigen was obtained from normal newborn kidney.

The globulin fraction from 2 individuals with acute nephritis, 3 with nephrotic syndrome, and 1 with lipoid nephrosis gave similar reproducible titers. No titer was below 1:40, with 1 at a level of 1:640. The sera of these patients showed more variation, but still remained above 1:40 and as high as 1:640. One nephrotic syndrome had been in remission for 6 months and 1 lipoid nephrosis was on steroids; they showed no significant serum reactions, although the globulin was 1:20 in the former. Three patients with nephrotic syndrome and 1 with lipoid nephrosis had positive reactions when the urine globulin was used with kidney antigen in the tanned red cell system in dilutions of 1:20 to 1:80. Sera, serum globulins, and urine from control subjects never showed titers greater than 1:20.

The modification of the tanned red cell technic using globulin appears more reliable and sensitive in detecting kidney antibody in the sera and also in the urine of patients with immune-type renal disease. By using the globulin portion of sera, the reproducibility of the test was improved, apparently by eliminating the effect of albumin in the reaction. It is suggested that the technic will be useful in investigating immune mechanisms in the production of disease, and may be of clinical importance in evaluating and following patients.

Atypical Renal Responses to Intravenous Hydralazine in Patients with Heart Disease

Robert Rosenblum, Jacob Grossman, and Louis Leiter, New York, New York

The renal hemodynamic effects of hydralazine (0.3 mg./Kg., intravenously) were measured during 16 studies in 14 subjects, in 6 of whom the cardiac output (CO) (Fick) was simultaneously determined. In 4 normal subjects, 1 patient with minimal rheumatic valvulitis without congestive failure and 2 patients (3 studies) with histories of failure, the usually described response, i.e., unchanged glomerular filtration rate (GFR) and increased renal plasma flow (RPF), was observed. The CO rose significantly (> 25 per cent) in all 3 of these subjects in whom it was measured. However, 5 other patients with past failure and similar clinical pictures, including initially depressed renal hemodynamics and CO, exhibited further reduction in GFR and RPF, although the CO increased significantly (> 25 per cent) in all 3 in whom it was measured. A repeated study in 1 subject resulted in a "normal" response. In 2 other subjects, 1 cardiac and 1 with depressed renal hemodynamics of uncertain origin, a simultaneous fall in GFR and rise in RPF occurred. Observed renal responses were not related to changes in arterial pressure or heart rate.

The renal response to intravenous hydralazine in cardiac patients is unpredictable. Since the CO rose in all cases, the observed reduction in RPF suggests that in some patients with previous failure, the renal vascular bed is unable to participate proportionately in hydralazine-produced generalized vasodilatation. Such increased renal vascular resistance is often reflected in the persistently disproportionately diminished RPF following therapy of early failure.

Lack of Correlation of Serum Cholesterol and Habitual Diet of Male and Female Adults

Ray H. Rosenman, Meyer Friedman, and Sarah Boasberg, San Francisco, California

Higher serum cholesterols (SC) of adults in the United States compared with less-privileged populations have been widely attributed to diet, particularly to higher fat intake. However, actual correlations of habitual diet and SC are lacking, prompting this study of 236 female and 251 male, white, urban, randomly selected white-collar workers, executives, and housewives, aged 30 to 59 years, having no major differences of physical activity. Each was bled for duplicate SC and carefully instructed in measuring and recording his total habitual food and cigarette consumption for 7 days. Average daily intakes of total calories, protein, carbohydrates, and total animal and per cent fats were calculated by the same experienced dietician. The SC of subgroups subdivided by age, decade, and sex were plotted against each diet factor, absolute and relative to body surface area.

SC and dietary intakes varied widely, as expected, but no relationship was found between them. SC varied widely at each dietary level; mean SC varied irregularly with increasing increments of any foodstuff and were closely similar at lowest and highest dietary intakes of any foodstuff, despite the latter's 4- to 5-fold differences. SC in each subgroup also were not related to weight, overweight, or cigarette consumption.

The data strongly suggest the presence of dominant factors other than habitual diet in the regulation of the concentration of SC and underlying the relatively high SC of urban, adult Americans.

Autoregulation of Coronary Blood Flow

John Ross, Jr., Paul W. Mosher, and Robert F. Shaw, New York, New York

Investigation of the coronary circulation is uniquely complicated because the characteristics of myocardial contraction not only determine the nutritional needs to be met by this circulation, but create the pressure head for coronary perfusion while simultaneously offering resistance to coronary flow. The interdependence of these parameters has resulted in a paucity of unequivocal information.

By means of a new preparation in which the open-chest anesthetized dog is maintained in steady cardiovascular state for extended periods while flow in a major coronary branch is suddenly altered by changes in coronary perfusion pressure, an intrinsic feedback mechanism has been demonstrated within the coronary bed.

In each of 374 observations in 12 experiments, a characteristic vasomotor response to pressure steps from control to perfusion pressures ranging from 20 to 240 mm. Hg occurred. Abrupt increase or decrease of perfusion pressure resulted in abrupt increase or decrease of flow; within 0.5 second, an active mechanism intervened to return flow toward its original level, and stabilized flow within 8 to 30 seconds.

Poststabilization steady-state pressure-flow curves constructed from these steps demonstrate: (1) complete compensation with independence of coronary flow from perfusion pressure within the range from 60 to 82 mm. Hg to 120 to 240 mm. Hg; (2) a linear relation between flow and pressure below 60 mm. Hg, with critical closing pressure at 15 to 27 mm. Hg; and (3) a correlation between the level of regulated coronary flow and cardiac work.

These studies demonstrate autoregulation within the coronary bed and suggest that coronary perfusion pressure per se is not a determinant of coronary blood flow in the physiologic pressure range.

Turnover Rates and Myocardial Extraction of Individual Free Fatty Acids

Martin E. Rothlin, Detroit, Michigan

The myocardial extraction of individual free fatty acids (FFA) has been estimated from the coronary arteriovenous differences of FFA level and the FFA composition in man and in dogs. Gas chromatographic analysis of FFA revealed a higher percentage of oleic acid and a lower percentage of palmitic and stearic acids in coronary sinus blood. The estimated absolute amounts of all individual FFA were lower in coronary sinus blood. Apparently, all individual FFA were extracted by the heart, but free oleic acid was removed at a higher rate. A similar study for adipose tissue showed that free oleic acid is also released at a higher rate. This suggests that free oleic acid may have a higher turnover rate in plasma than other FFA. An increase of the arterial FFA level induced by norepinephrine indicates predominant release of FFA; a decrease of the arterial level induced by glucose and insulin suggests their predominant uptake. As arterial FFA decline, the percentage of oleic acid diminishes, that of palmitic and stearic acids increases. The reverse changes occur during an increase of arterial FFA. It is concluded that the preferential uptake of free oleic acid by the heart reflects a higher turnover rate of free oleic acid in plasma.

Effects of Isoproterenol on Pulmonary Vascular Resistance in Pulmonary Hypertension

George C. Roveti, T. David Lee, and Richard S. Ross, Baltimore, Maryland

Isoproterenol has been found to reduce pulmonary vascular resistance (PVR) in 9 patients with severe pulmonary hypertension (pulmonary artery [PA] mean pressure ranging from 51 to 105 mm. Hg). The pulmonary hypertension was "primary" in 2 patients, secondary to scleroderma in 1, and secondary to congenital heart disease in the remaining 6.

Measurements of pulmonary blood flow and pulmonary arterial pressure were made before and 15 minutes after the sublingual administration of 10 to 20 mg. of isoproterenol. Oxygen consumption was measured and the Fick method used for the determination of pulmonary blood flow in the 7 patients with circulatory shunts; the indicator-dilution technic was employed in the remaining 2.

Pulmonary blood flow was increased following isoproterenol in all cases. The average increase was 28.6 per cent of the control value, or 0.63 L./min./M.^{2} (range 0.26 to 1.23 L./min./M.^{2}). The mean PA pressure remained constant in 8 of the

9 patients studied. The PVR decreased (average: 5.76 mm. Hg/L./min./M.^{2}). No significant hemodynamic changes were observed in 1 patient with normal PA pressure and PVR.

In this study, isoproterenol increased cardiac output and pulmonary flow. In 8 of the 9 patients, this increase in flow was not accompanied by an increase in PA pressure. These results indicate that isoproterenol produced pulmonary vasodilation in addition to an increase in cardiac output in these patients with severe pulmonary hypertension of diverse etiology.

Systemic and Coronary Hemodynamic Effects of Chlorothiazide and a New Pteridine Diuretic

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2,4,7-Triamino-6-phenyl pteridine has been introduced recently as an aldosterone-inhibiting diuretic. Since the hemodynamic effects of the compound are similar to those of chlorothiazide, the present comparison of their effects in man is presented.

Cardiac output was measured by the Fick principle and coronary blood flow by the nitrous-oxide method. Studies were done before, and approximately 1 hour after, administration of each drug. 2,4,7-Triamino-6-phenyl pteridine was administered orally in a single 300-mg. dose, whereas chlorothiazide was administered intravenously in a 500-mg. dose. Both agents are known to be active in the period of time studied, and the results reported are those of acute effects.

In general, administration of each drug tends to be associated with a decrease in central venous pressure and a decrease in cardiac output. Since peripheral blood pressure did not change significantly, the calculated peripheral resistance increased. Coronary blood flow did not change significantly, whereas left-ventricular work tended to decrease.

Chlorothiazide is reported to be helpful in some subjects with angina pectoris; presumably this may be related to decreased left-ventricular work with maintained coronary blood flow. The effects of 2,4,7-triamino-6-phenyl pteridine on angina are not yet established.

Quantitative Anatomy of the Normal Child's Heart

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Measurements of orifices, thicknesses of walls, internal wall dimensions of chambers, and weights of entire heart and parietal walls of chambers were carried out on 83 normal autopsied hearts of children from zero to 15 years of age. Twenty-one variables were studied using age, weight, and length of child as the independent variables.

The relationship between the independent variables and the thickness of the right ventricle, and of the left ventricle at the apex, was found to be constant, the formula being $y = c$, where (c) is a constant. For the weights of the parietal walls and of the entire heart, the line of best fit obeys the formula $\log y = b \log x + \log a$. The relationship for all other variables was represented by the equation $y = b \log x + a$, where (a) is a constant, (b) the slope of the best-fitting line, (y) the value of the variable, and (log x) the log of either age, length, or weight.

Multiple correlations with the log of age, weight, and length were calculated for all variables. The regression equation for variable (i) takes the form:

$$X_i^1 = B_A \frac{\sigma_i}{\sigma_A} X_A + B_W \frac{\sigma_i}{\sigma_W} X_W + B_L \frac{\sigma_i}{\sigma_L} X_L +$$

$$\left[M_i - B_A \frac{\sigma_i}{\sigma_A} M_A - B_W \frac{\sigma_i}{\sigma_W} M_W - B_L \frac{\sigma_i}{\sigma_L} M_L\right],$$

where X_A, X_W, X_L represent, respectively, the log of age, weight, and length for a particular subject; M_A, M_W, M_L the means of the log of age, weight, and length; σ_A, σ_W, σ_L the standard deviation of the same variables; B_A, B_W, B_L the corresponding multiple regression weights; σ_i and M_i the standard deviation and mean of the variable (i) that is being predicted; and X_i^1 is the predicted value for variable (i). Thus, one can predict the normal value of any heart modality in a child of certain age, height, and weight.

Study of Right Atrial Pressure-Pulse in Patients with Functional Tricuspid Regurgitation and Normal Sinus Rhythm

George A. Rubeiz and Ibrahim K. Dagher, Beirut, Lebanon

Right atrial curves obtained on patients with unquestionable tricuspid regurgitation and normal rhythm are rare. Six patients with tight mitral stenosis and normal sinus rhythm were studied. Ages ranged from 26 to 39 years; there were 4 females and 2 males. They all had grade II to grade IV systolic murmurs that increased with inspiration, best heard between the cardiac apex and the left lower sternal border. This was confirmed by logarithmic phonocardiograms obtained during expiration and inspiration. Electrocardiograms revealed atrial and right-ventricular hypertrophy in all cases. In 5, right-heart catheterizations were performed. In all 6 patients, right atrial pressure-pulse was obtained with a 20-gage needle introduced in the right atrium during right thoracotomy. The diagnosis of functional tricuspid regurgitation was established by digital exploration

of the tricuspid valve immediately after the pressure recording. Subsequently, mitral commissurotomy was performed.

Right atrial pressure-pulses obtained at right-heart catheterization and those obtained with the needle were comparable. In 5 patients, the X-descent of the right atrial pressure-pulse was deeper than the Y-descent. In only 1 case was the X-descent equal to the Y-descent. There was no exaggeration of the V wave in any of the curves.

It is concluded that in functional tricuspid regurgitation with normal rhythm, the normally preserved X-descent followed by a normal V wave may persist in the right atrial curve. The application of this finding to the clinical study of the jugular venous pulse in functional tricuspid regurgitation and normal rhythm is evident.

Observations on a Sphincter Mechanism at the Pulmonary Venous–Left Atrial Junction

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A muscular envelope extending from the left atrium onto the pulmonary veins has been implicated as possessing a sphincter action. A pressure gradient between the pulmonary veins and the left atrium has been demonstrated in various situations. The possibility that this gradient was due to partial obstruction of the pulmonary vein by a large catheter was considered.

Small polyvinyl catheters were placed directly into the upper (O.D. 0.035 inch) and the lower (O.D. 0.050 inch) pulmonary veins of mongrel dogs. In some experiments, catheters were placed facing upstream and downstream in the same vein. A catheter was also placed directly into the left atrium. Studies were made in closed-chest animals breathing spontaneously under a number of experimental conditions.

A small mean gradient of 0 to 2 mm. Hg between pulmonary vein and left atrium existed under control conditions. No difference was observed between pressures in the upstream or downstream catheters under any circumstances. An increase in the pulmonary vein–left atrial gradient was produced by: occlusion of the opposite pulmonary artery; hypoxia; epinephrine, serotonin, or hypertonic-saline infusion; opening of an artificial aortopulmonary shunt. The changes were more prominent in the upper and middle than in the lower pulmonary veins.

In order to separate active vasomotion from flow dependency in the establishment of this gradient, the effects of sympathetic blocking agents were observed. In the preparations with controlled aortopulmonary communications, the gradient was completely abolished both with the shunt closed and open, after tetraethylammonium chloride administration. These studies indicate that there is an active vasomotion at the junction of pulmonary vein and left atrium.

Serum Cholesterol and Master Two-Step Test Responses in Coronary Patients Receiving Hypocholesteremic Agents: Thyroid Extract, Dextrothyroxine, Dextrotriiodothyronine, Linoleic and Arachidonic Acids, and Triparanol

Henry I. Russek, Staten Island, New York

Results of treatment with hypocholesteremic agents in 137 patients with various forms of clinical coronary-artery disease are presented. Duration of each course of therapy varied from 6 months to 3 years. The greatest and most persistent lowering of blood cholesterol was observed with triparanol and dextrothyroxine. Linoleic- and arachidonic-acid preparations produced a significant response in less than 25 per cent of the patients treated and actually caused a paradoxical marked elevation in 20 per cent. Thyroid extract, administered slowly in steplike dosage up to 3 gr. daily, exhibited little effect on serum-cholesterol levels. No improvement in exercise-electrocardiographic (Master 2-step) tests was observed among patients treated with triparanol, even after 1 year of such therapy. Dextrothyroxine increased the frequency of anginal attacks in 4 patients and produced acute coronary insufficiency in 2. These side effects were considered to have been caused by too high an initial dosage or too rapid an increase from starting levels. Exercise tolerance and electrocardiographic response to stress were distinctly improved in some patients when the dosage of dextrothyroxine was altered in steplike increments. Dextrotriiodothyronine was found to produce hypermetabolism in a high percentage of the patients treated and was associated with increase in anginal symptoms and deterioration of the exercise-electrocardiographic response. To date, dextrothyroxine and triparanol, individually or in combination, appear to offer the greatest promise for the control of hypercholesterolemia. Additional benefits appear possible from the use of dextrothyroxine.

Emotional Stress and Coronary Heart Disease in American Physicians and Dentists (P)

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The finding in previous studies that coronary heart disease in young adults is commonly associated with emotional stress of occupational origin suggested a survey of the prevalence of this disease among professional groups encountering varying

degrees of daily occupational stress. Among physicians, 4 groups were chosen for analysis: dermatologists, pathologists, anesthesiologists, and general practitioners. In addition, dentists in the category of general practitioners were also selected for study. The prejudged stressfulness of occupational responsibilities in the respective categories resulted in the following ranking (in order of increasing stress): dermatology, pathology, dentistry, anesthesiology, general practice. The prevalence of coronary heart disease was determined from a questionnaire survey of 5,000 male subjects, 1,000 in each of the above categories. Among the respondents, a close correlation was found between the prejudged stressfulness of the occupational groups and the actual coronary heart disease prevalence. This was observed in every age decade from 40 to 69 and was found to be highly significant statistically. In sharp contrast, arterial hypertension showed an almost identical distribution in all 5 categories studied, suggesting that this disease is apparently not a stress disorder, but one which is genetically linked.

Evaluation of Drug Therapy in Angina Pectoris Employing the Master Two-Step Test: Vasodilators, Amine Oxidase Inhibitors, and Hypocholesteremic Agents

Henry I. Russek, Staten Island, New York

No current method of evaluation provides as informative and reliable data as exercise-electrocardiographic tests in the evaluation of drug response in patients with angina pectoris. This technic has been applied to determine coronary-myocardial responses in 75 carefully selected patients with predictable electrocardiographic control records. Of numerous alleged vasodilator agents evaluated, only nitroglycerin, pentaerythritol tetranitrate, erythrol tetranitrate, isosorbide dinitrate, theophylline (elixir), and papaverine have been associated with favorable responses. The amine oxidase inhibitors have been responsible for a varying incidence of symptomatic improvement, depending on potency of the individual agent. With none, however, have subjective responses been correlated with comparable benefit in electrocardiographic tests. Triparanol has not been associated with improvement in exercise-electrocardiographic tests, despite significant hypocholesteremic effects maintained for 1 year or more. Dextrothyroxine in doses initially too high has evoked marked increase in the degree of abnormality observed in exercise-electrocardiographic responses. With careful titration to avoid hypermetabolism, however, significant improvement in exercise-electrocardiographic tests has been observed.

Influence of Injection Site upon Observed Flow Relationships Between Right and Left Ventricle (P)

Thomas J. Ryan, John H. Williams, Jr., and Walter H. Abelmann, Boston, Massachusetts

In 12 patients without intrinsic lung disease, 17 simultaneous determinations of right ($\dot{Q}_{RV}$) and left ($\dot{Q}_{LV}$) ventricular output were made by a single injection of indicator into superior vena cava, sampling from pulmonary and brachial arteries. $\dot{Q}_{RV}$ exceeded $\dot{Q}_{LV}$ by a mean difference of 6.1 per cent $\dot{Q}_{LV}$, S.D. 9.7. The mean difference between duplicate determinations was 14.6 per cent $\dot{Q}_{LV}$, S.D. 5.8. In these same patients, when indicator was injected into the left atrium and sampled from the brachial artery and a second indicator injected, less than 30 seconds later, into the superior vena cava and sampled from the pulmonary artery, $\dot{Q}_{LV}$ exceeded $\dot{Q}_{RV}$. The mean difference, 7.4 per cent $\dot{Q}_{LV}$, S.D. 11.4, significantly differed from that obtained by the former method ($P < 0.01$). The mean difference between duplicate determinations in 7 patients by the latter method was 5.3 per cent $\dot{Q}_{LV}$, S.D. 5.8, indicating a significantly greater ($P < 0.01$) reproducibility by this method.

These data suggest that right-sided indicator injections underestimate $\dot{Q}_{LV}$. Indicator injected as a bolus into the superior vena cava had a passage time in the pulmonary artery exceeding 6 seconds. Consequently, its "duration of injection" into left atrium consistently exceeded the known appearance time of left atrium to brachial artery. Thus, the prerequisite of instantaneous injection was no longer met. Elimination of the right heart and lungs from the volumes traversed by indicator used to measure $\dot{Q}_{LV}$ significantly reduced the spread of the curve and, hence, the opportunity for distortion by slow injection or recirculating indicator.

Relationship Between Age and Serum-Cholesterol Level at the Time of First Episode of Myocardial Infarction

Marvin L. Sachs, Terry L. Bartolet, and Orville Horwitz, Philadelphia, Pennsylvania

As part of an effort to characterize patients with diagnoses of "arteriosclerosis," 500 consecutive inpatient records signed out as myocardial infarction without diabetes mellitus were screened. Only those cases with no previous diagnosis of myocardial infarction and with a serum-cholesterol determination during the admission were included. Cases of familial hypercholesterolemia were excluded. This left a total of 208 males and 66 females in the "infarct group," ranging in age from 35 to 87 years. These were compared with a con-

trol group of 412 males between the ages of 26 and 69 years who had serum-cholesterol determinations at the time of a careful study which revealed no evidence of arteriosclerotic heart disease. The entire infarct group had higher cholesterol levels than the control group, the difference being greater in the earlier ages and falling to an insignificant average of 2 mg./100 ml. in the 60- to 64-year age group. However, when the infarct group was restricted to the 208 males, the cholesterol levels were found to be distinctly *lower* than the controls beyond the age of 56 years. Beyond the age of 60 years, there was a 14 mg./100 ml. average difference. Others have reported that the serum-cholesterol levels taken after myocardial infarction have little prognostic significance. In this study, the cholesterol levels were determined at the approximate time of the infarction rather than at a later date in patients with a history of myocardial infarction. These results support the idea that in the age groups above 55 to 59 years, serum cholesterol has little diagnostic significance in the nondiabetic male, and encourage speculation that arteriosclerosis may be different in young and old people.

Measurement of Effective Circulating Volume and Total Circulating Volume in Normovolemic Hemorrhagic Shock

Joseph M. St. Ville and William C. Shoemaker, Chicago, Illinois

Wiggers, as well as many other investigators studying shock, has defined the critical problems of normovolemic shock as lack of effective circulating volume. The purpose of this study, therefore, was to measure the effective circulating volume (ECV) and relate it to the total circulating volume (TCV). Measurable differences between the 2 are taken to represent the portion of circulating blood which is "sequestered."

A known volume of Cr^{51}-labeled red cells was injected into dogs under control conditions, after hemorrhage and after retransfusion (normovolemia). A constant sampling of blood was passed through a NaI well scintillation counter, and the radioactivity of the samples was graphically recorded. The volume of dilution in 10 minutes was taken as the ECV and the final volume of dilution was taken as the TCV. Tracings were made under control conditions, after hemorrhage by the Wiggers technic and following retransfusion of the shed blood.

The above procedures were carried out on 25 mongrel dogs. ECV and TCV were found to be the same in normovolemic dogs and in the dogs in hypovolemic shock. On retransfusion, however, a definite difference could be consistently demonstrated between the ECV and the TCV.

A definite difference has been demonstrated between the ECV and the TCV in dogs in normovolemic shock induced by bleeding. This delay in the equilibration of tagged cells with the entire blood volume is taken as evidence of sequestration of a portion of the blood volume or removal of a portion of the cellular elements from the effective circulation during normovolemic shock.

Simultaneous Systemic-Arterial and Intracardiac Indicator-Dilution Curves

Philip Samet, William H. Bernstein, and Leonard Silverman, Miami Beach, Florida

Elucidation of the presence and localization of varied types of right-to-left intra- and extracardiac shunts has been greatly facilitated by indicator-dilution curves obtained from systemic arteries and the right heart. Simultaneous recording from these 2 sites is of further value. Indicator-dilution curves in varied types of congenital and acquired heart disease will illustrate these points.

Differential right and left pulmonary left-to-right shunting occurs in anomalous pulmonary-venous drainage without an interatrial septal defect, in most cases with the ostium secundum type of interatrial defect, and in subjects with the sinus venosus variety of atrial defect. These 3 congenital lesions are readily distinguished by indicator-dilution curves obtained by insertion of 2 cardiac catheters into the right heart. Differential right-to-left systemic-arterial shunting in subjects with patent ductus arteriosus and severe pulmonary hypertension is readily evaluated by indicator-dilution curves obtained from the brachial and femoral arteries. Localization of acquired systemic arteriovenous fistulas and congenital left-to-right shunts is feasible by insertion of 2 right-heart catheters with downstream injection distal to the shunt and intracardiac sampling both upstream and downstream of the shunt, or with upstream injection proximal to the shunt and intracardiac sampling both upstream and downstream of the shunt.

New Prosthetic Valve Designs and Material for Aortic and Mitral Valves

Luis H. Sanchez, Minneapolis, Minnesota

Combined use of hypothermia with the pump-oxygenator makes it possible to meet the metabolic demands of the tissues with greatly reduced perfusion rates. This has been found advantageous in the much longer periods of bypass needed at present for prosthetic valve replacement.

Many cardiovascular surgeons have come to appreciate the necessity of adequate prosthetic valves for replacement, partially or completely, of de-

stroyed valves. Although much previous work, experimental and clinical, has been reported on this subject, there exists great need for improvements in prosthetic valves.

Our experimental and clinical work with various designs and materials has led us to the selection of certain materials and designs. Aortic valves have been constructed of polyurethane, Estane 5700X101-5CS2337, and of daeron coated with silastic rubber. The design is tricuspid in type without a rigid annular ring. Fabric rims around the cusp provide tissue ingrowth, and a firm attachment to the original root of the aortic valve, together with the free edges of the 3 cusps meeting each other at the same level, secures adequate coaptation which gives a definite advantage anatomically and hemodynamically, and thus prevents stenosis or regurgitation.

Mitral valves were fabricated of the same materials. The design duplicated that of normal mitral valves, but without chordae tendineae. Pressure recordings and ventriculograms were taken to show adequate function with no stenosis or insufficiency.

Long-term survivals (4 months) have indicated properties of polyurethane as the ideal material for prosthetic valve construction among materials we have tested. It is non clot-forming, has long flex life, and is strong and durable.

Relationship of Left-Ventricular Volume to Tension, Stress, and Pressure in Man (P)

Harold Sandler, Harold T. Dodge, and Robert E. Hay, Seattle, Washington

The time course of diastolic left-ventricular (LV) pressure (LVP), volume (LVV), and wall tension and stress was compared in 7 human subjects with valvular heart disease. LV-chamber dimensions, wall thickness (h), and changes in these parameters were determined from rapid biplane angiocardiograms. LVV and volume changes were calculated from the angiocardiograms and varied from 72 to 448 cc. end-diastolic volume. LVP was recorded at or immediately before angiocardiography, with end-diastolic pressure varying from 6 to 60 mm. Hg. Tension (T) and stress (T/h) were calculated along the maximal principle radii of curvature (r_1, r_2) of the LV chamber by assuming that the LV could be represented as an ellipsoid of revolution and applying Laplace's law as follows: $\frac{T_1}{r_1} + \frac{T_2}{r_2} = P$. End-diastolic tension varied from 23×10^3 to 265×10^3 dynes/cm. and stress from 20×10^3 to 380×10^3 dynes/cm.^{2}. Individual diastolic tension-volume and stress-volume curves were comparatively more steep than the pressure-volume curves. Thus, as ventricular volume increased, tension and stress acting on the ventricular muscle increased considerably more rapidly than pressure, which may increase only slightly, and resulted in a relatively flat pressure-volume curve. The forces acting in the ventricular wall to stretch the ventricular muscle during diastole are a function of ventricular pressure, volume, and shape, and this study represents an attempt to quantify these relationships.

Effects of Ventricular Overload on the Pathway of Ventricular Depolarization and on the QRS Complex

Toyomi Sano, Tokyo, Japan, and Allen M. Scher, Seattle, Washington

As the first step in a continuing study of electrocardiographic abnormalities associated with alterations in ventricular hemodynamics, we have studied conduction changes associated with partial occlusion of the pulmonary artery and aorta. A number of multipolar electrodes were inserted in the ventricular wall and control records were taken. When the right-ventricular systolic pressure was raised to 60 to 100 mm. Hg, there was a delay in the depolarization of the right wall and usually of the right septum. The pattern of depolarization and magnitude of the delay showed that this phenomenon was not right bundle-branch block. At times, this delay in conduction amounted to 8 msec. (20 to 25 per cent of QRS duration), while at other times the delay was less. This conduction delay was only at times associated with electrocardiographic alterations characteristic of right-axis deviation (moderate right-ventricular strain pattern—late negativity in leads II and III).

In preliminary studies, increased left-ventricular systolic pressure produced conduction delay in the periendocardial region of the left wall. No significant QRS changes were noted, except for occasional ectopic beats.

Chronic partial constriction of the pulmonary artery in 2 dogs produced electrocardiographic changes (increased positivity in V_1) which are consistent with either altered conduction or change in heart size or position. These animals will be examined to see if conduction has been altered.

Visualization of Small Left-to-Right Shunts by Contrast-Media Injection into the Main Pulmonary Artery

C. Glenn Sawyer, Robert N. Headley, Henry S. Miller, Lawrence B. Leinbach, and James F. Martin, Winston-Salem, North Carolina

Laboratory confirmation of the existence and location of suspected small septal defects has proven difficult in the presence of inconclusive blood oxygen content changes. Indicator-dilution technics are not easily performed in infants and

small children. The injection of contrast media directly into the left heart by retrograde arterial, percutaneous, or transseptal approaches is not without hazard. The need for a simplified method of detection and localization of equivocal septal defects has become evident.

After completion of the right-heart catheterization, a NIH dye catheter was introduced via the same peripheral vein and advanced to the main pulmonary artery. Warmed sodium diprotrizoate and sodium diatrizoate solution was employed as the radiopaque medium in an approximate dosage of 1 cc./lb., with a maximal single dose of 35 cc. A bolus injection was accomplished within 1 second by a Taveras Injector developing a maximum pressure of 1,075 lbs./in.^{2} at syringe outlet.

Passage of the opaque media through the pulmonary vasculature and left heart was recorded on Eastman shellburst film at 60 frames/sec. by a 16-mm. camera attached to an 8-inch Picker image orthicon. For demonstration of an atrial septal defect, the right-anterior oblique position is optimal; an 80-degree, left-anterior oblique projection is most satisfactory for detecting dye traversal of the ventricular septum.

To date, no complications have been encountered with injection of the dye either into the main pulmonary artery or at its bifurcation. Pressure injection of the dye into a distal pulmonary artery radical can be dangerous. This technic, if properly executed, provides a safe, simple, right-heart approach to the detection of small septal defects.

Hemodynamic Response to a Controlled Aortopulmonary Anastomosis

Emile M. Scarpelli, Norman L. Gootman, Richard J. Golinko, and Abraham M. Rudolph, New York, New York*

The acute adjustments to a controlled aortic-pulmonary-arterial shunt were studied in 25 mongrel dogs. A silicone-rubber prosthesis, through which flow could be regulated, was inserted between the main pulmonary artery and the descending aorta. Electromagnetic flowmeters were used to monitor aortic flow. Pressures in various sites were measured by direct catheter placement. The acute changes following opening and closing of the shunt were studied postoperatively in the closed-chest animal, breathing spontaneously. Pulmonary-systemic flow ratios with the shunt open were 2.5:1 to 4:1. Pulmonary-arterial, left-atrial, and left-ventricular diastolic pressures all increased.

The following responses were observed on opening the shunt. Forward flow in the distal aorta was decreased, and there was a marked increase in backflow during diastole. Forward flow in the ascending aorta increased without any significant change in backflow. A systolic gradient between left ventricle and aorta was established in some animals. The duration of right-ventricular systole was markedly reduced, and pulmonary-valve closure occurred well before aortic closure. A characteristic pulmonary-arterial pulse contour with 3 systolic peaks was observed.

The effects of tetraethylammonium (TEA) and norepinephrine infusion on adjustments to opening and closing of the shunt were studied. With the shunt open, norepinephrine infusion produced an increase in aortic flow and pressure. Left-ventricular diastolic pressure was, however, markedly reduced. After TEA, opening of the shunt was not tolerated and a progressive increase in left-ventricular diastolic pressure and a decrease in left-ventricular stroke volume occurred. These effects could be reversed by norepinephrine infusion.

Cardiorespiratory Dynamics During Ventricular Asystole in Dogs with Complete Heart Block

Emile M. Scarpelli, New York, New York, and Madison S. Spach, Durham, North Carolina

Ventricular asystole was studied in 11 dogs in which complete heart block was produced by ligation of the atrioventricular bundle. Ventricular rate was artificially maintained for 4 to 14 days postoperatively, at which time ventricular asystole was produced by cessation of stimulation. NH_4Cl was infused to obtain suitably long periods of asystole up to 40 seconds. The effects of apnea and positive-pressure respiration were also studied.

In studies of 392 periods of ventricular asystole with independent atrial activity, the following results were obtained: (1) right atrial to pulmonary artery flow at a rate of 121 to 130 ml./min. was seen within 3 seconds after the onset of asystole; (2) left atrial to aorta flow did not begin until aortic pressure fell to left atrial pressure levels or below; (3) atrial waves, representing "flow pulses," were recorded in the aorta; (4) apnea and positive-pressure breathing significantly reduced these time-flow patterns; (5) there was regurgitation from left ventricle to left atrium across the mitral valve; (6) there was a left atrial to pulmonary artery pressure gradient during atrial systole, and a reverse gradient during early diastole; (7) inspiration favored the pulmonary artery pressure in relation to left atrial pressure, while expiration, apnea, and positive-pressure breathing had the reverse effect; (8) respiratory rate, tidal volume, total airway resistance, and respiratory work were increased; (9) compliance, functional residual capacity, and work efficiency were decreased; and (10) there was a

marked decrease in end-tidal CO_2 levels to 3 to 5 mm. Hg.

Abdominal Aortic Aneurysms: Reappraisal (P)

Irwin J. Schatz, John F. Fairbairn, II, and John L. Juergens, Rochester, Minnesota

Re-evaluation of the criteria for recommendation of surgical excision of abdominal aortic aneurysms is necessary. One hundred and forty-one patients with this disease who had not been operated upon were seen from 1950 through 1959. Surgical treatment was not recommended for 114, and 27 refused operation when surgical treatment was recommended. Follow-up information was obtained from 137 patients (97 per cent). Of 119 patients, 87 per cent survived 1 year, 52 per cent survived 3 years, and 36 per cent survived 5 years after diagnosis. These results are compared with the survival of normal members of the population of the same mean age, and also with the results of a previous study by Estes. Of patients who had a history of cardiac disease at the time of diagnosis of aneurysm, 75 per cent survived 1 year, 33 per cent survived 3 years, and 20 per cent survived 5 years. Of those without such a history, 96 per cent survived 1 year, 63 per cent survived 3 years, and 50 per cent survived 5 years.

Forty-six patients were known to have died during the follow-up period. The cause of death was rupture of the abdominal aortic aneurysm in 19 patients (44 per cent); 24 patients (56 per cent) died of other causes (these are listed). Of the patients who died and who had no histories of cardiac disease at the time of diagnosis of the aneurysm, none died of myocardial infarction.

Survival rates in this study have been compared with those in another study of 400 surgically treated patients seen during the same period. Factors to be considered in the selection of patients for operation upon their abdominal aortic aneurysms are discussed in the light of newer knowledge concerning the prognosis for these patients.

Effects of Coronary-Artery Catheterization and Coronary Angiography upon Left-Ventricular Contractile Force and Myocardial Oxygen Tension

Robert C. Schlant, Thorne S. Winter, III, Fuat Birkardesler, Young W. Cho, and Naci Bor, Atlanta, Georgia

Catheters were introduced via the carotid artery into the left anterior descending or circumflex coronary artery of open-chest dogs. In 12 dogs, this resulted in immediate ventricular fibrillation. In 20 dogs, it was possible to record the following sequential changes as ischemia developed: (1) an average maximum decrease in left-ventricular contractile force of 55 per cent from the control value of 15 mm. scale deflection occurred in 244 seconds and reached one-half of the maximum decrease in 130 seconds; (2) an average maximum decrease in left-ventricular-tissue oxygen tension of 62 per cent from the control value of 33 mm. scale deflection occurred in 341 seconds and reached one-half of maximum decrease by 153 seconds; and (3) there usually were S-T segment alterations in the epicardial electrocardiogram. The administration of contrast material through the catheter produced additional significant decreases in contractile force and myocardial oxygen tension. Perfusion of blood through the catheter rapidly reversed toward control values the changes produced by catheter introduction and, to a lesser extent, by contrast-material injection. These studies demonstrated rapid significant changes in contractile force and myocardial oxygen tension resulting from coronary-artery catheterization in dogs, exaggeration of these changes by injection of contrast material, and reversal of these changes after perfusion of the catheter with blood. It is suggested that the perfusion of blood through a catheter in the coronary artery would be of value in the interval between introducing the catheter and obtaining a coronary angiogram.

Cardiopulmonary Telemetry

Thomas A. Schulkins and George H. Sullivan, Van Nuys, California

This program was developed for the study of the effects of space travel on man. Animals were prepared to transmit data from simulated space and, eventually, orbital flight. The first step in the program was the building of a transistorized unit that would transmit an electrocardiogram. This unit was then placed in the abdomen of a dog which transmitted to a monitoring device. Further, dogs were used to refine electrodes, their sites, and mode of implantation. After feasibility was proven, the study was transferred to simians; rhesus monkeys were used. In 5- to 7-pound monkeys, units were placed that were capable of transmitting a single-channel electrocardiogram. There were no external connections from these animals to the monitoring device. The transistorized units could be recharged through the intact skin. Space couches were constructed and animals were placed in centrifuge to simulate space flight at 12-G forces. In addition, 2-G forces of vibration were added. Through all this testing, the animals transmitted essentially normal electrocardiograms for this species. The study now has progressed to adding a phonocardiogram and intrapleural pressure to the transmitted data.

The same size rhesus monkeys were used. The sensing devices, a transmitter, and an antenna for recharging are all internally implanted in the animal. Data can be received on a monitoring device 50 feet away, and from there be retransmitted to unlimited distances. We feel that this technic lends itself to the study of other environmental situations.

Late Systolic Murmurs

Bernard L. Segal, Daniel Mason, Hratch Kasparian, and William Likoff, Philadelphia, Pennsylvania

Leatham classified systolic murmurs into ejection and pansystolic murmurs. Pansystolic murmurs at the apex are consistent with mitral regurgitation. Late apical systolic murmurs have been considered innocent physiologic murmurs. Six patients are reported in whom a late apical systolic murmur was present with mild to moderately severe mitral regurgitation. The phonocardiogram showed the crescendo murmur to begin in midsystole and end with aortic-valve closure. The left-atrial pressure curve showed a sharp "y" descent with no end-diastolic gradient, and selective left-ventricular angiography demonstrated 2-plus mitral regurgitation.

Third Heart Sound in Mitral-Valve Disease

Bernard L. Segal, Daniel Mason, Paul Novack, and William Likoff, Philadelphia, Pennsylvania

In patients with mixed lesions of the mitral valve, difficulty arises as to which lesion is dominant. When the phonocardiogram taken at the mitral area demonstrates a third heart sound (0.12 to 0.16 second after aortic-valve closure), this finding is suggestive of a dominant mitral regurgitation. Twelve patients with a loud third heart sound with clinical evidence of both mitral stenosis and regurgitation were studied by left-heart catheterization and selective left-ventricular angiography. In 10 patients, the mitral-orifice long diameter measured 1.8 to 2.4 cm.^{2}, and no end-diastolic gradient was present. Selective left-ventricular angiography demonstrated regurgitation into the left atrium. The finding of the third heart sound in a patient with mixed mitral-valve disease is suggestive of a dominant mitral regurgitation.

Auscultatory and Phonocardiographic Findings Following Open-Heart Surgery for Mitral Stenosis

Bernard L. Segal, Paul Novack, and Daniel Mason, Philadelphia, Pennsylvania

Past experience has indicated that in the majority of patients, the major auscultatory and phonocardiographic evidence of mitral stenosis persists following closed-heart surgical correction. It has been the contention that these persistent abnormalities were not a reflection of the failure to obtain hemodynamic benefit, but had their origins in a relatively inconsequential valvular deformity. The auscultatory and phonocardiographic findings following open-heart surgery were compared with the preoperative findings in 30 patients.

In contrast with the experience of closed-heart technics, the following changes were observed: (1) the first heart sound remained loud but of less intensity; (2) the opening snap frequently disappeared; (3) in most patients the apical diastolic rumble was absent; and (4) there was a distinct decrease in the frequency of the apical pansystolic murmur of mitral regurgitation.

There was a good correlation of the hemodynamic and auscultatory findings following the correction of the mitral stenosis by the open-heart method. From the evidence cited, it appears that the persistence of abnormal auscultatory findings in patients operated for mitral stenosis represents inadequate correction of the lesion.

Arteriosclerotic and Hypertensive Cardiovascular Disease in Patients with Hyperparathyroidism

Jack P. Segal and John J. Canary, Washington, District of Columbia

Thirteen patients with hyperparathyroidism were clinically evaluated to determine if arteriosclerotic heart disease and hypertensive vascular disease are more frequent in this endocrinopathy. There is published clinical and experimental evidence that diseases associated with hypercalcemia may, by deposition of calcium in the arterial wall, accelerate the arteriosclerotic process.

The diagnosis of hyperparathyroidism was established in 13 patients and confirmed by surgery. There were 8 males and 5 females, from 37 to 63 years of age. Cardiovascular diagnoses were: arteriosclerotic heart disease in 2; hypertensive arteriosclerotic heart disease in 1; hypertensive heart disease in 3; and unexplained cardiac enlargement in 1. In 2 patients, nonspecific electrocardiographic findings were present in the absence of cardiovascular symptoms or cardiac enlargement; first-degree atrioventricular block was present in 1, and voltage criteria for left-ventricular hypertrophy in the other. Four patients were hypertensive without evidence of heart disease. Hypertension was present in a total of 8 patients, 7 having nephrolithiasis and/or nephrocalcinosis. Three patients had nephrolithiasis without hypertension. Serum cholesterols were elevated in 3 of 7 patients, and serum uric acids were elevated in 5 of 10 patients.

In summary, 11 of 13 patients had definite heart disease or hypertension, and the remaining 2 had nonspecific electrocardiogram changes. There appears to be an increased incidence of arteriosclerotic heart disease and hypertensive heart disease in patients with hyperparathyroidism. Probably, patients with hypertensive and/or arteriosclerotic heart disease, particularly in the younger age group, should be evaluated for hyperparathyroidism.

Activation of Left-Ventricular Epicardium Before and After Left Ventriculotomy and After Left Bundle-Branch Block

Martin Seidenstein, Jackson H. Stuckey, and Robert S. Venerose, Brooklyn, New York

By utilizing cardiopulmonary bypass and surface electrodes, the activation sequence of the epicardial surface of the left ventricle was studied in dogs before and after left ventriculotomy and also before and after left bundle-branch block. An 8- to 10-cm. longitudinal ventriculotomy incision was performed through the midportion of the left ventricle, care being taken not to compromise the major blood supply of the ventricle. Block was obtained by transecting the left common bundle. Electrical activity at the surface electrodes was monitored on an oscilloscope and photographed on paper moving at 200 mm./sec. The temperature of the dog was monitored by a thermistor and was kept constant throughout the experiments; lead II of the standard electrocardiogram was also monitored.

Following left ventriculotomy, no delay or change in sequence occurred in the activation of the epicardium of the left ventricle. Following left bundle-branch block, the pattern of epicardial activation was changed, the earliest points being adjacent to the interventricular grooves anteriorly and posteriorly, and becoming progressively more delayed toward the midportion of the left ventricle. Thus, it would appear that following left bundle-branch block, the epicardial surface of the left ventricle adjacent to the interventricular grooves is activated by impulses passing from the right ventricle, while the more centrally located portion is activated either by conduction in muscle or delayed local reactivation of Purkinje fibers.

Combined Administration of Chemically Different Diuretic Agents (P)

Robert H. Seller, Morton Fuchs, Albert N. Brest, and John H. Moyer, Philadelphia, Pennsylvania

In order to determine whether an additive or synergistic diuretic action could be obtained by the simultaneous administration of chemically different diuretics, the following clinical outpatient study was performed. A group of 24 patients in congestive failure was studied. Half received hydrochlorothiazide, 200 mg. daily for 3 weeks; then chlorthalidone, 200 mg. daily, was added for 3 weeks. The other half received the same drugs, but in reverse order. The combined effects of meralluride and trichlormethiazide were also investigated in the same group of patients. Frequent evaluations of their clinical status and serum electrolytes were performed.

Bio-assay studies including the effect on serum and urinary electrolytes were also determined in a group of hospitalized patients. The combined diuretic regimens listed above were studied. In some cases spironolactone was added.

This study revealed that these agents have a significant additive and/or synergistic activity, even when each is administered at its maximum effective dose. Combinations of these chemically different diuretics produced a significantly greater weight loss and natruresis than the maximum effective dose of any of these agents alone. Side effects included nausea and vomiting, muscle cramps, and digitalis toxicity.

It was concluded that the administration of combinations of chemically different diuretics produced a significantly greater diuresis than a single agent. These observations suggest the efficaciousness of this form of therapy in refractory edema states in addition to other routine measures.

Preliminary Report of Use of Renal Biopsy as a Diagnostic Aid in Hypertensive Patients (P)

Alfred M. Sellers, Eugene A. Hildreth, and Joseph S. Handler, Philadelphia, Pennsylvania

Since July, 1960, 41 hospitalized hypertensive patients have been subjected to renal biopsy and culture in a search for occult pyelonephritis and for definitive diagnosis of the type of renal disease present. All subjects had recent onset of hypertension, and urine cultures obtained prior to biopsy were negative. One or 2 biopsy specimens were obtained from each kidney studied. In a few patients, renal biopsies were performed bilaterally. Bacterial cultures were obtained of the kidney and urine collected after biopsy. Except for expected microscopic hematuria, no untoward complications occurred.

Sixteen patients presented either normal renal histology or arteriolar nephrosclerosis. Eight had lesions of chronic glomerulonephritis. Three patients fulfilled all 3 of our criteria for pyelonephritis: positive histologic evidence, positive renal culture, and positive postbiopsy urine culture. In 14 patients, either biopsy disclosed pyelonephritis

or culture was positive, but since all 3 diagnostic criteria were not met, they are classified "renal status indeterminate."

In pyelonephritic patients, treatment of hypertension was deferred during the period of antibiotic therapy so that blood pressure alterations might better be interpreted. Pyelonephritis was treated with antibiotics, selected on the basis of in vitro sensitivity tests, for 1 month, followed by 3 months' treatment with a long-acting sulfa compound. Repeat urine culture was negative at this time.

Preliminary results suggest favorable influence on early hypertension following energetic treatment of pyelonephritis. The prognostic significance of renal lesions diagnosed by this technic may aid in planning long-term management of the hypertensive patient, whether the lesions are pyelonephritis, glomerulonephritis, nephrosclerosis, or other.

Timed Vectorcardiogram and Electrocardiogram in 107 Proven Cases of Interatrial Septal Defect

Ronald H. Selvester, L. Julian Haywood, Donald E. Griggs, and Richard P. Boggs, Los Angeles, California

The timed vectorcardiogram is of value in the differentiation of right-ventricular hypertrophy and right bundle-branch block. In the present study, we have reviewed 13-lead electrocardiograms and timed vectorcardiograms of 107 cases of proven interatrial septal defect (100 septum secundum and 7 septum primum).

In the electrocardiograms, 88 per cent of P waves were normal; 12 per cent showed left-atrial enlargement. In the timed vectorcardiograms, only 19 per cent of these P waves were normal, 46 per cent had right-atrial enlargement, 30 per cent combined atrial enlargement, and 5 per cent left-atrial enlargement alone.

The QRS forces were normal in 7 per cent of the electrocardiograms; 14 per cent revealed an rSr′ in V_1 with an RS ratio less than 1 (the so-called incomplete right bundle-branch block) and did not meet Sokolow's and Lyon's criteria of right-ventricular hypertrophy. Sixty per cent had an rsR′ or predominant R in V_1 and met these criteria. Nineteen per cent had complete right bundle-branch block. The timed vectorcardiograms revealed 2 per cent with normal QRS forces, 5 per cent incomplete right bundle-branch block, 57 per cent right-ventricular hypertrophy, and 36 per cent complete right bundle-branch block. Nine patients had left-axis deviation in addition to RsR′ in V_1; 7 of these had a septum primum at open-heart surgery, 2 had uncomplicated septum secundum defects.

Conclusions: (1) The timed vectorcardiogram will aid in the diagnosis of specific atrial enlargement and will differentiate right-ventricular hypertrophy and right bundle conduction defects; (2) incomplete right bundle-branch block per se in interatrial septal defect is an uncommon finding; (3) left-axis deviation with a superior directed QRS loop in the frontal plane does occur in uncomplicated secundum-type atrial septal defects.

Rapid Analysis of Indicator-Dilution Curves for Intracardiac Shunts

Ronald H. Selvester, L. Julian Haywood, and Philip Reiswig, Los Angeles, California

Indicator-dilution curves have proven of value in diagnosis of intracardiac shunts. To detect small shunts and calculate cardiac output, a semilog plot of the concentration of indicator at any sampling site plotted against time must be made; in patients without shunts, a straight-line exponential downslope after the initial peak is observed. A method is presented which, in many cases, eliminates the necessity of the semilog plot to indicate the presence of a shunt, and which therefore speeds diagnosis.

From the Cartesian-coordinant tracing, the concentration of the peak and first valley of the dilution curve can be readily measured and a ratio calculated which will be directly proportional to the presence and size of a left-to-right shunt.

Fifty patients with left-to-right shunts were compared with 50 patients without shunts. Over 200 curves were analyzed. If the peak-to-valley ratio was 5 or less, there was a 98 per cent chance of left-to-right shunt; when the ratio was 10 or greater, there was a 98 per cent chance that no shunt was present—three-fourths of each group was detected by this means. When the ratio is between 5 and 10, 50 per cent of patients may have shunts.

Organic heart disease other than left-to-right shunts did not disturb results and there was no direct relationship to cardiac output. Results were less reliable in very young children; patients in frank heart failure were not included. This method offers a simple and rapid method of detecting the presence of a definite left-to-right shunt at the time the curve is obtained.

Factors Influencing Changes in Pulmonary-Vascular Resistance in Mitral-Valvular Disease (P)

Arthur Selzer, San Francisco, California, and Robert O. Malmborg, Stockholm, Sweden

In a series of 8 patients with mitral stenosis, serial hemodynamic studies were performed and changes in calculated pulmonary-vascular resist-

ance (PVR) observed and correlated with clinical changes and other hemodynamic parameters. In 5 patients, serial studies demonstrated a 4- to 10-fold increase in PVR over a 2- to 3-year period. Only in 2 of the 5 cases did this change in PVR coincide with a significant increase in mitral-valvular obstruction. In 5 cases, following a significant surgical relief of mitral-valvular obstruction, a fall in PVR of appreciable magnitude was observed. These 5 cases constitute all patients in a consecutive series in whom marked elevation in PVR was present before the operation and significant surgical result was obtained following valvotomy.

Observations reported in this study are reviewed in the light of present concepts of the nature of elevated PVR. The consistently observed reduction in PVR that follows the relief of mitral-valve obstruction shows convincingly the role of left-atrial hypertension in sustaining high PVR. However, observations concerning the development of high PVR demonstrate that left-atrial hypertension is not the sole stimulus for the development of high PVR in mitral stenosis. It is concluded that chronic or intermittent elevation of left-atrial pressure constitutes the background for the development and the sustenance of high PVR, but that other factors trigger this abnormal pulmonary-vascular reaction.

Heart Volume Determined by Surface Counting

Gunnar Sevelius, James R. Snider, and Daniel R. Patrick, Jr., Oklahoma City, Oklahoma

A monitored volume of blood expressed in milliliters can be estimated by dividing the counts recorded by surface counting with counts per milliliter aliquot. When the heart region is monitored, an expression for heart volume can be determined. The heart monitoring is done with a 2-inch crystal without collimation. Five μc. of radioiodinated serum albumin is used as a tracer substance. The blood aliquot is counted in a well counter. A conversion factor of the counts from the well counter to the heart monitor for different sensitivities and geometries is received from a group of patients by assuming a known monitored heart volume as suggested from an x-ray film. A conversion factor of 1:33 is used in our system. This was used to calculate the monitored volume in the group reported below.

In 17 patients with heart volumes ranging from 1,600 to 600 ml. by x-ray and the formula of Rohrer, there was a correlation coefficient of 0.87 with the heart volumes determined by surface counting. The mean of the heart volumes determined by x-ray was 967, and was 890 ml. by surface counting. In 2 patients with pericardial perfusions, a comparison between the x-ray shadow and the monitored volume could establish the diagnosis.

Acute and Chronic Changes in Peripheral Resistance Following Surgical Constriction of the Anterior Descending Coronary Artery in the Dog

William H. Sewell, Oteen, North Carolina

The proximal anterior descending coronary artery was constricted in 75 dogs in an effort to produce distal hypotension for a study of factors influencing the stimulation of intercoronary collateral channels. The distal pressure was measured through a PE 50 catheter inserted in a distal branch. Although the constriction reduced the pressure by as much as 50 per cent of the control level, the pressure usually spontaneously returned to normal in about 20 minutes.

Because of this unexpected finding, acute experiments were done with an orifice-type flowmeter to study the coronary peripheral resistance. This resistance was found to increase gradually after the proximal artery was constricted. Temporary complete occlusion of the artery resulted in profound vasodilation, and this change was spontaneously reversed in 5 to 10 minutes.

In another series of dogs, relative flow in the anterior descending coronary artery, as compared with the circumflex, was estimated by using coronary cinearteriography without arrest in pre- and postoperative dogs. The pressure in the anterior descending coronary artery was measured through a catheter.

This experiment showed that the dogs had practically a normal distal pressure if the proximal anterior descending coronary artery was constricted so that between 20 and 40 per cent of the normal lumen area remained open. However, these dogs had an approximately 50 per cent reduction in the flow as compared with preoperative studies. These observations indicated that the distal anterior descending coronary artery had vasoconstricted enough to maintain its peripheral resistance considerably above normal in the postoperative dogs.

Physiologic and Technical Requirements for Experimental Strong Stimulation of Coronary Collateral Arteries

William H. Sewell, Oteen, North Carolina

Previous experiments on 140 dogs have shown that neither ligation of the anterior descending coronary artery, occlusion by thrombus in a polyethylene graft in this artery, nor constriction of the same vessel by a plastic device physiologically similar to Vineberg's ameroid was very satisfactory for stimulating the formation of intercoronary

arterial channels. There was a relatively high mortality, and many animals got infarcts which required less arterial supply than the functioning myocardium that was replaced. Study showed that a procedure that will not stimulate intercoronary collateral channels is very unlikely to stimulate many collaterals from a pedicle.

In recent experiments on 55 dogs, consistently strong stimulation was satisfactorily obtained only if the area of the lumen of the proximal anterior descending coronary artery was first reduced to between 4 and 10 per cent of normal, and was later completely occluded. Mortality and infarcts resulted if the initial constriction was too tight. If it was too loose, adequate collateral did not develop to protect against the subsequent occlusion.

A technic was developed for consistently constricting the artery into the required range. The pressure in the distal anterior descending coronary artery was monitored through a PE 50 catheter and was used as an indication of the degree of constriction produced. The plastic device began to constrict the artery more tightly about 1 week postoperatively, and occlusion was complete about 2 weeks later.

Coronary cinearteriography and corrosion casts were used to demonstrate the partial and complete obstructions of the major vessels and the development of collateral channels between them.

Use of Coronary Cinearteriography for Estimation of Relative Flow in the Anterior Descending Coronary Artery After Experimental Surgery in Dogs

William H. Sewell, Oteen, North Carolina

Coronary arteriograms were performed on 280 dogs with the hearts beating normally. Technical factors included the use of an 8-inch image amplifier, 35-mm. fine-grain film, a 0.5-mm. focal-spot x-ray tube with a triple-speed rotor, radiographic magnification, exposure time of one two-hundredths of a second on each frame, 30 frames per second, and high-contrast developer. High-contrast prints were made on 16-mm. movie film and lantern slides. Contrast media were injected into the left sinus of Valsalva.

The relative diameter and rate of movement of contrast media in the anterior descending coronary artery was measured from the films and compared with measurements of the circumflex before and after surgical constriction of the anterior descending artery. After appropriate geometric corrections, the postoperative flow in the anterior descending artery could be expressed as a percentage of the preoperative ratio. Study of 220 measurements showed that the results are reproducible, with a standard deviation of about 5 per cent.

The experiments showed that a mild proximal constriction of the anterior descending coronary artery was followed by a decrease in the diameter of the distal artery without change in the relative velocity within it. A tighter constriction was followed by both a decrease in the diameter and a lower relative velocity.

Hypotension in the distal artery did not occur unless the relative flow was reduced by more than about 50 per cent of the preoperative level, but was found consistently with flow below that. Collateral arterial channels did not form between the circumflex and the anterior descending artery unless the diastolic pressure was reduced by about 20 mm. Hg for at least 5 to 7 days. The degree of hypotension was roughly correlated with the amount of collateral which formed.

Hemodynamics of Cardiac Tamponade

Ralph Shabetai,† Noble O. Fowler, and Mosche Gueron, Cincinnati, Ohio

Thirty-one dogs were prepared by thoracotomy and their chests were closed. Saline was injected into their pericardial sacs until marked inspiratory decline in blood pressure (pulsus paradoxus) was recorded.

In 6 dogs pressures recorded from an extrapericardial pulmonary vein and the left atrium failed to reveal a decrease in gradient from vein to atrium during inspiration when systolic arterial pressure declined.

In 4 dogs no change in gradient between superior vena caval and right atrial pressure accompanied inspiratory decrease in systemic arterial pressure.

In 3 dogs the effluent from the subclavian artery was pumped by a proportioning pump to a femoral artery and the descending aorta was occluded below the left subclavian artery. Blood pressure fell during inspiration in the ascending aorta, and to a lesser extent in the descending aorta. In 11 dogs the respiratory variations in pressure were opposite in direction in the aorta and pulmonary artery.

In 6 dogs aortic pressure and flow measured by an external electromagnetic flowmeter were recorded. The inspiratory fall in aortic blood flow and pressure in the control state was greatly enhanced during tamponade.

Conclusions: Pressure studies did not demonstrate that pulsus paradoxus was caused by difficulty in filling the atria. The normal respiratory variation in blood pressure is partially independent of alterations in aortic blood flow. Even during cardiac tamponade, inspiration was associated with increase of pulmonary arterial pulse pressure. The systemic blood pressure variations of pulsus para-

doxus due to cardiac tamponade are associated with comparable alterations in aortic blood flow.

Complete Heart Block and Ventricular Standstill in Rheumatoid Arthritis

William Shapiro, Elam C. Toone, Jr., Robert Irby, and Hawey A. Wells, Jr., Richmond, Virginia

Complete heart block, asystole, and death in rheumatoid arthritis (RA) has been reported only twice, and rheumatoid nodules in the septum appeared to be responsible in those cases. We have seen 2 middle-aged women in whom this or other known causes for heart block could not be found.

Case I had mild RA for 12 years and developed a brief, reversible, episode of block. Three months later, it suddenly recurred with frequent episodes of ventricular standstill. Within 28 hours, she became refractory to therapy, including the external pacemaker, and died. Case II had severe RA for 30 years. Forty-eight hours prior to death, she developed complete block with frequent ventricular standstill. Although initially responsive to isoproterenol, the ventricular focus became refractory to all therapy and the patient died. Heart disease had not previously been present in either patient. Chloroquine had been given to both, and case II had steroid therapy.

Necropsy demonstrated areas of swollen myocardial fibers with cigar-shaped vacuoles in the perinuclear regions containing coarse basophilic granules. This has been described as basophilic degeneration of the myocardium and was severe in case I, mild in case II. These changes have not been thought to be responsible for cardiac dysfunction, and may have been secondary to the preterminal therapy and/or ischemia. The possibility remains, however, that these degenerative alterations were related to the fatal arrhythmias observed in our patients.

Role of Pulmonary Megakaryocytes in Development of Increased Blood Coagulability and Arterial and Venous Thromboses

J. George Sharnoff, Mount Vernon, New York

Our recent animal and human studies disclosed that there exists a cell phenomenon capable of causing increased systemic blood coagulability and, under already existing conditions, of inducing arterial and/or venous thrombosis. These studies support the belief of Wessler and others that increased coagulability of blood is the most important of Virchow's triad in the etiology of thrombosis.

The cell phenomenon is the tremendous, continuous, transient reservoir of 150,000 or more pulmonary megakaryocytes ever ready suddenly to release many millions of freshly formed platelets into the systemic circulation. The resulting sudden platelet increase was found to be associated with a marked shortening of blood coagulation time and occasional thrombosis, coronary artery and leg veins, the latter terminating in pulmonary embolism. Evidence indicated that the degree of increased blood coagulability paralleled the rise in platelets and was dependent on the number of megakaryocytes present at any given time in the pulmonary sinusoids. The greater the number of megakaryocytes, the greater the increase. Also, these blood values change rapidly under changing conditions. Clinical and laboratory evidence disclosed that periods of immobilization of individuals is the greatest single factor causing an accumulation of pulmonary megakaryocytes which are then pounded up into platelets on resumption of physical activity or any form of stress, by a sudden increase in heart rate and blood pressure. The degree of platelet increase and increased blood coagulability along with the other factors of the triad may determine the site of thrombosis.

Respiratory Mechanics and Total Work of Breathing in Extreme Obesity

John T. Sharp, John P. Henry, William R. Meadows, and Stanford K. Sweany, Hines, Illinois

Six obese subjects (251 to 367 lbs.) including 2 patients with the obesity-hypoventilation (O-H) syndrome were investigated. In addition to conventional pulmonary function testing, total respiratory mechanics and work of breathing were studied using a tank respirator as first described by Otis, Fenn, and Rahn.

Both patients with the O-H syndrome had low lung compliance, low thoracic compliance, and low total respiratory compliance (0.055 and 0.070 L./cm. H_2O). Of the 4 obese patients without the O-H syndrome ("normal" obese subjects), 2 had reduced lung compliance and 1 had reduced thoracic compliance, giving 3 of the 4 with either reduced or borderline total respiratory compliance.

Total respiratory resistance was increased (16 and 21 cm. H_2O/L./sec.) in both patients with the O-H syndrome and in 2 of 4 "normal" obese subjects. Thoracic (tissue) resistance was increased in both patients with the O-H syndrome and in 1 of the 4 "normal" obese subjects. Pulmonary resistance was normal in 1 patient with the O-H syndrome and moderately increased in the other, although in this patient no clinical or other physiologic signs of obstructive pulmonary disease were present. Pulmonary resistance was slightly increased in 2 of the 4 "normal" obese subjects.

The total work of breathing was increased in

both patients with the O-H syndrome (2.5 to 5 times normal) and in 2 of the "normal" obese subjects.

In the heaviest patient with the O-H syndrome, the natural frequency and inertance of the respiratory system were measured. The former was 3.1 c.p.s. (normal, 5 to 12 c.p.s.), the latter 0.038 cm. H_2O/L./sec.^{2}, about 6 times normal.

Comparison of I^{131}–Iodohippurate Sodium Renogram with Intravenous Pyelogram, Aortogram, and Howard Test in Hypertension

Alton R. Sharpe, Jr., Richmond, Virginia

Analysis of the I^{131}–iodohippurate sodium renogram utilizing the $T\frac{1}{2}$ excretion time as an index of renal function is a useful diagnostic procedure.

Sixty-seven male subjects (12 normal and 55 with hypertension) have been studied. Mean $T\frac{1}{2}$ time for the normal group was 6.5 minutes, with a range from 3 to 15 minutes. Fifteen hypertensive subjects were studied utilizing 3 or more of the conventional methods. Seven of this group had abnormal renograms characterized by $T\frac{1}{2} > 15$ minutes. Five of this latter group had abnormal aortograms, 4 had positive Howard tests, and 3 had abnormal pyelograms. Of 3 patients selected for surgery, 1 had normal renal artery pressure, 1 had abnormal pressure and bilateral arteriolar disease, and 1 had abnormal pressure and unilateral disease. The latter patient became normotensive following nephrectomy. Nephrectomy was not performed in the other 2.

Analysis reveals 4 distinct iodohippurate sodium uptake and excretion patterns: (1) normal uptake and excretion; (2) normal uptake and bilateral abnormal excretion; (3) normal uptake and delayed excretion on 1 side; and (4) normal uptake on 1 side and abnormal uptake and excretion on the opposite side.

Patients with 1 of the latter 3 patterns should have further diagnostic studies. The data suggest that the I^{131}–iodohippurate sodium renogram is an accurate and valuable diagnostic tool in assessing hypertension.

Sequential Exercise Cardiac-Output Responses in Thyroid Diseases

Alton R. Sharpe, Jr., and William Shapiro, Richmond, Virginia

The cardiac index (CI) recovery pattern after exercise has not been studied in thyroid disease. The reliability of the precordial isotope-dilution technic has made rapid serial CI studies readily available with minimum patient manipulation. Five normal, 11 myxedematous, and 6 thyrotoxic subjects performed the Master single 2-step test and CI was determined before, immediately, 5 minutes, and 10 minutes after exercise. Thyroid status of patients was proved by conventional function tests. The patients had no evidence of heart disease. Euthyroid mean CI pattern at these times was 2.8, 5.5, 3.4, and 3.0 L./min./M.^{2}. Myxedema mean CI pattern was 2.9, 4.2, 2.9, and 2.9 L./min./M.^{2}. Thyrotoxic mean CI pattern was 4.3, 4.9, 5.2, and 4.5 L./min./M.^{2}.

The pulse rates were followed in 6 subjects and mirrored the CI responses. Recovery in myxedema was similar to that in euthyroid subjects, but the response to exercise was less. The magnitude of exercise response in the toxic group was also less, but more sustained in time. Such patterns may well reflect the presumed differences in catecholamine sensitivity between these groups. These responses may be useful in clinical evaluation of hyperthyroidism.

Relation of Anaerobic Myocardial Metabolism to Left-Ventricular Failure (P)

Thomas M. Shea, Richard M. Watson, Stanley F. Piotrowski, George Dermksian, and Robert B. Case, New York, New York

The left main coronary artery of the dog was perfused by a Sigmamotor pump with blood supplied from the femoral artery. Coronary insufficiency was produced by a stepwise reduction in the rate of coronary flow. Pressure was measured continuously in the right atrium, left atrium, aorta, and in the coronary perfusion tubing distal to the pump. Aortic blood pressure was held constant by the addition of donor blood when necessary. Arterial and coronary-sinus blood samples were analyzed for oxygen and lactate. Coronary vascular resistance was calculated at each step.

In all six dogs, the results showed the onset of a negative A-V lactate difference, occurring after coronary vascular resistance had fallen to a minimum value. The maximum output of lactate during the period of insufficiency varied from 0.8 mg./min. to 8.5 mg./min. for the series, but remained at a steady level for any given dog. The appearance of a negative A-V lactate difference was accompanied in all the animals by a rise in left-atrial mean pressure. With further reduction in coronary flow, a progressive rise in left-atrial pressure up to 40 mm. Hg occurred, but the negative A-V lactate difference was not correspondingly increased. When coronary insufficiency was produced in a different manner, by raising arterial pressure while coronary flow was maintained constant, similar changes in lactate production were noted.

These findings indicate that anaerobic myocardial metabolism may occur in the normotensive well-oxygenated animal subjected to an inadequate coronary flow and that the onset of this type of metabolism is accompanied by myocardial failure.

Analog Computer Use for Immediate Determination of Phasic Power and Mean Energy Expenditure in Arterial Blood Flow (P)

Richard B. Shepard, Birmingham, Alabama

Power-producing blood flow, or instantaneous rate of energy expenditure, has been determined at the aortic root, in the terminal aorta, and in the femoral artery, in various combinations, in 10 dogs. This was done in an investigation of the hypothesis that phase differences between pulsatile flow and pressure, if varied, may result in significant changes in energy requirements for flow without necessarily changing mean flow and mean pressure. In 4 animals, simultaneous measurements of blood flow with electromagnetic flowmeters, and of blood pressure at the same sites, were made concurrently in the aortic roots and terminal aortas. Instantaneous values of pressure and flow were corrected for zero, scaled, and then multiplied by an analog computer. This product is taken to represent rate of energy dissipation in the vascular tree distal to the site of measurement. Integration with respect to time yielded beat-by-beat work totals for the vascular tree distal to each site. In the aortas of normal dogs, rate of energy expenditure was found to follow the blood-flow curve closely. Time interval between power peaks in the aortic root and the terminal aorta varied from 0.05 second to 0.09 second, being greatest after administration of acetylcholine. Delivery of power to the aorta from the legs was observed in diastole under normal operative conditions, and during diastole following the first systole after acetylcholine cardiac arrest. Reverse power transmission was not observed in the femoral artery of an animal with its aorta lengthened 10 inches.

New Type of Antithrombotic Effect of Monamine Oxidase Inhibitor Compared with Anticoagulant

Takio Shimamoto, Tadao Ishioka, and Tsutomi Fujita, Tokyo, Japan

We discovered a new type of antithrombotic effect of monamine oxidase inhibitor which prevents the phylogenetically old hemostatic process, but not directly the phylogenetically young fibrinogen-fibrin system.

In this experiment, thrombosis was produced in central arteries and marginal veins of rabbit ears by quantitative traumatization of endothelial surface with a dental hand reamer inserted into the vessel lumen and crushing with a type of paper holder. The evaluation of results was performed 1 to 2 to 5 days after traumatization grossly, histologically, and statistically.

In 23 control rabbits, 58 of 92 traumatized vessels were occluded by thrombosis. In 23 rabbits pretreated daily by a single dose of 50 to 100 mg. of oral phenindione 2 to 4 days before and after challenge and showing a percentage prothrombin under 10 per cent, 35 of 92 vessels were occluded. In 23 rabbits pretreated by 5 mg./Kg. of oral nialamide 2 to 4 hours before challenge and exhibiting no appreciable change in Quick's prothrombin time, Lee-White time, and bleeding time, only 12 of 92 vessels were occluded.

Histologic exploration revealed that nialamide prevents sticking and agglutination of platelets to injured endothelium which forms a white thrombus-dam; this dam contributes to the prevention of the washing away of clotting factors into the blood stream.

In this experiment on 69 rabbits, the preventive effect of nialamide against experimental thrombosis was found to be much stronger as compared with phenindione, and this difference is statistically significant ($P < 0.001$). In addition, nialamide, unlike the anticoagulants, did not prevent extravascular clotting.

Application of Antithrombotic Effect of Nialamide in Arteriosclerotic Disorders Including Myocardial Infarction

Takio Shimamoto, Hiroh Yamazaki, Hiromichi Tsuchihashi, Toshiaki Sunaga, and Tadao Ishioka, Tokyo, Japan

Our findings on monamine oxidase inhibitor led us to perform clinical trials on nialamide as an antithrombotic drug. A nialamide dose possibly capable of preventing thrombosis was determined by its preventive effect against the immediate decrease in platelet count (Olef) by intravenous epinephrine (0.1 μg.), by oral fresh cream (90 cc.) plus butter (5 Gm.), or by Master's test in 95 adults, according to our experimental findings.

Decrease in platelet count by these procedures was prevented by oral administration of nialamide by single doses of 100 mg. in 91 per cent of cases tested, but in 43 per cent with 50 mg.; and in 81 per cent with 75 mg. daily, but in 23 per cent with 50 mg.

Of 27 patients suffering from acute transmural myocardial infarction in our hospital in 1960 to 1961, 15 control patients (3 females, 12 males, aged 43 to 74 years, hospitalized on odd days) were treated ordinarily, with 5 dying. The remaining 12 patients (males, aged 45 to 77 years, hospitalized on even days) were given 100 mg. of

nialamide initially, and thereafter 25 mg. 3 to 4 times daily, all surviving without relapses.

For 2 to 73 weeks, 109 patients (aged 45 to 77 years) suffering from arteriosclerotic disorders were on oral nialamide, 50 to 100 mg. (mostly 75 mg.) daily, and none developed thrombosis. Also, there was no hypotensive or hepatotoxic response in serial determinations of liver function tests, serum alkaline phosphatase, thymol turbidity, zinc thymol turbidity, C.C.F., SGO-T, and SGP-T, except in 1 patient suffering from cardiac liver cirrhosis in whom thymol turbidity (1.0, 10.0) and zinc thymol turbidity (14.0, 24.0) worsened temporarily. There was no abnormality in Quick's prothrombin and Lee-White times, Duke's bleeding time, nor in von Borbely's test. Nialamide is worthy of being tested further as an antithrombotic drug.

Some Properties of Enzymes Released into Human Plasma by Heparin (P)

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In addition to the glyceride moieties of some serum low-density lipoproteins, a number of unemulsified mono- and diglycerides of C_{16} and C_{18} fatty acids and the mono-, di-, and triglycerides and ethyl esters of C_4 and C_6 fatty acids were substrates in vitro for lipolytic and esterolytic enzymes which were released into human plasma after intravenous injection of heparin. The unemulsified triglycerides and ethyl esters of C_{16} and C_{18} fatty acids were not hydrolyzed; triacetin and trioctanoin were hydrolyzed very slowly, if at all, at pH 8.3. All heparin-released lipolytic and esterolytic activities were inhibited by diisopropyl fluorophosphate, diethyl-p-nitrophenylphosphate, *l*-thyroxin, and *l*-triiodothyronine; eserine inhibited none. The nonionic detergent, Triton X-100, inhibited only lipolysis of lipoproteins. Dialysis of the plasma against 0.15 M NaCl and 0.002 M ethylenediaminetetraacetate at pH 7.6 reduced the rates of fatty-acid release from lipoproteins and diolein, but did not alter fatty-acid release from *l*-monoolein, trihexanoin, or monobutyrin. Unlike the lipolysis of lipoproteins, the hydrolyses of monoolein and glycerides of short-chain fatty acids were not inhibited by fatty-acid accumulation. The heparin-released activities for hydrolysis of pure glycerides persisted after all activity for lipolysis of lipoproteins had been destroyed by heating the plasma at 52 C. for 15 minutes.

It appears that heparin releases into plasma more than 1 enzyme which may be involved sequentially in glycerol and fatty-acid production from triglycerides transported by some low-density lipoproteins. The mono- and diglyceride intermediates need not be in a lipoprotein complex for hydrolysis.

Serum Enzyme Elevation in Shock

Herbert Shubin and Max H. Weil, Los Angeles, California

Elevation of serum glutamic oxaloacetic transaminase (SGOT) in patients with shock does not necessarily indicate that the acute circulatory failure is caused by myocardial infarction. SGOT, serum glutamic pyruvic transaminase (SGPT), and lactic dehydrogenase (LDH) concentrations were determined in patients with shock due to hemorrhage, bacterial infection, or neurogenic cause. Care was taken to exclude all patients with any evidence of primary liver or heart disease. Of the total of 43 patients studied, 21 were ultimately excluded for these reasons.

Elevations of SGOT were observed in 12 of the 22 patients, SGPT in 6 of 20, and LDH in 8 of 20. The average value of elevated SGOT on the first day of shock was 70 units. In patients in whom transaminase increased, continuation of shock was accompanied by further elevation, and recovery from shock by reduction of the transaminase value. Increases of SGPT were noted only in patients who had increases of SGOT. However, in 3 of the patients, elevation of LDH alone was observed. No significant correlation between SGOT elevation and survival was demonstrated.

Vasopressor agents were used in the treatment of 18 patients. Elevations of SGOT occurred in 10 of these 18 patients. Eight patients who received comparable doses of norepinephrine and metaraminol had normal SGOT values. These findings do not support the hypothesis that SGOT elevations are induced by vasopressor therapy.

Choice of Operation for Pulmonary Valvular Stenosis

Harris B. Shumacker, Indianapolis, Indiana

Operative experiences with treatment of 84 patients with pulmonary stenosis and proved, or presumably intact, ventricular septum were analyzed in order to determine the best method of treatment. Forty-seven were treated by closed valvulotomy. They all survived. Six of them were very ill infants treated as emergencies, and 4 others were treated as urgent cases. They did well. Catheterization studies indicate that earlier closed valvulotomies were often inadequate. On the other hand, later experiences with modification of the closed method indicate that excellent relief of the obstruction has been obtained. Thirty-seven were treated by open valvulotomy with total cardiopulmonary bypass. Among them there were 6 instances requiring treatment for muscular outflow

obstruction, 2 for infundibular stenosis, 8 for secundum-type atrial defects, and 1 for septum primum defect with cleft mitral valve. All survived and did well, save for 2 patients in whom there was present a diminutive and generally hypertrophied ventricle, both of whom died. Six similar cases did well when treated by the closed method.

It is felt that the closed method, modified so as to ensure adequate valvulotomy, is the procedure of choice when very ill infants must be operated upon as emergencies and for those with a diminutive hypertrophied ventricle. For the others, it is felt that the open method is preferable. It permits a more precise valvulotomy and the accurate repair of associated lesions. Transverse pulmonary arteriotomy provides exposure of the pulmonary valve superior to that obtained through the vertical incision used in the past.

Tricuspid Insufficiency as a Component of Congestive Cardiac Failure (P)

Bruce C. Sinclair-Smith, Walter Puckett, and Elliot V. Newman, Nashville, Tennessee

Systolic pulsations of the liver and the deep cervical veins are accepted signs of tricuspid insufficiency. The frequent presence of these physical signs in patients with congestive cardiac failure has suggested that incompetency of the tricuspid valve contributes to the venous hypertension of the congested state.

To test the validity of this hypothesis, tricuspid-valve function has been studied by indicator-dilution technics in clinical circumstances where increased right-atrial pressure exists (congestive cardiac failure of varying etiology, pericardial effusion, and constrictive pericarditis). Multiple injections of cardio-green dye have been made into the right ventricle while simultaneous sampling from the right atrium and a systemic artery has been carried out using a specially designed continuous-suction pump. Concentration of cardio-green dye has been determined by using a densitometer cuvette system in each of the sampling lines. The data obtained indicated that:

1. Significant tricuspid insufficiency (50 per cent of forward flow) occurs only in the presence of organic deformity of the valve.

2. No evidence of tricuspid insufficiency was obtained in patients with congestive cardiac failure who demonstrated abnormal neck-vein pulsation.

3. Marked tricuspid insufficiency can occur without any evidence of systemic venous engorgement.

4. The impairment of the x descent and the rapid y descent of the jugular phlebogram or right-atrial pressure trace are not reliable signs of tricuspid insufficiency.

5. The currently accepted signs of tricuspid insufficiency are no longer reliable in all circumstances.

The implications of these findings are discussed in relationship to the mechanism of venous hypertension of congestive cardiac failure and the effect of atrial fibrillation on atrioventricular-valve closure.

Surgical Risk in the Cardiac Patient

Jack Skinner, Denver, Colorado, and Morton L. Pearce, Los Angeles, California

The problem of evaluating operative risk in cardiac patients is a difficult one for surgeon, anesthetist, and physician. Several reports would suggest that the overall increase in mortality is small.

The plan of the study reported here was to employ electronic data processing to study 25 parameters in 867 operations in which preoperative cardiac consultations were available. The parameters studied involved the extent and duration of surgery and the type and severity of heart disease.

The overall mortality in these patients was twice that of the general hospital population undergoing surgery. All the cardiac patients did well in minor surgical procedures, including herniorrhaphy and transurethral resection. However, in major thoracotomies and laparotomies, the overall mortality was 25.4 per cent of 268 patients. The following 3 categories were the most sensitive for predicting mortality; the numbers in parentheses are the totals:

1. Etiology—rheumatic heart disease, 11 per cent (18); arteriosclerotic heart disease, 23 per cent (156); hypertensive heart disease, 26 per cent (92); pulmonary heart disease, 50 per cent (12).

2. Functional class—I, 11 per cent (9); II, 20 per cent (201); III, 42 per cent (59); IV, 100 per cent (1).

3. Special electrocardiographic features—atrial fibrillation, 28 per cent (29); left bundle-branch block, 54 per cent (11).

Comparative Evaluation of Nicotinic Acid and Other Forms of Therapy in Hyperlipemia and Hypercholesterolemia

Burton S. Sklarin, Winnifred Seegers, and Kurt Hirschhorn, New York, New York*

There is, as yet, no single ideal therapy for all cases of hyperlipemia or hypercholesterolemia. A rational approach to effective therapy must be based on a proper differential diagnosis between these 2 diseases, since therapy effective in one frequently is useless in the other.

Primary hypercholesterolemia is treated most effectively with nicotinic acid, with a minimum of toxic effects. A small group of patients, however, is resistant to doses of as much as 9 Gm. per day. Substitution of polyunsaturated fats for other dietary fats is practical and safe, but the mild effectiveness, although statistically apparent, is of questionable clinical significance in marked hypercholesterolemia. Unsaturated fats as a dietary additive are of little value. Treatment with estrogens or thyroid analogs has been disappointing and marked by side effects, while acetate competitors and sitosterols have been ineffective. We reserve triparanol for the rare patient in whom nicotinic acid is ineffective, and only when the therapeutic risk seems justified.

In the therapy of primary hyperlipemia, we have occasionally been successful with dietary management. In severe cases, we combine an initial period of fat-free diet with spaced-fat feeding, while mild cases are placed on spaced-fat feedings from the beginning. If the patient does not respond sufficiently, he is placed on nicotinic acid, which produces prompt and sustained lowering of triglyceride and cholesterol levels. Heparin given parenterally is effective in the heparin-sensitive lipemic, but its disadvantages make its use unnecessary where an effective alternative method is available. Sublingual heparin has proved disappointing.

Photoscanning of the Kidney in Hypertension (P)

David M. Sklaroff, Philadelphia, Pennsylvania

Chlormerodrin labeled with radiomercury is concentrated sufficiently by physiologic mechanisms to delineate the kidneys. By means of photoscanning, it is possible to obtain images of the kidneys. This is a recent development in diagnostic medicine.

In our brief experience with this procedure, images were obtained which suggest a fundamental usefulness in the preliminary screening of hypertensive patients where a suspicion existed of underlying renal disease.

This material is picked up by the renal tubules and, in cases of impairment of circulation, there is a decrease in concentration and a fainter image is produced on the "scan." Several cases of unilateral renal disease associated with hypertension have been demonstrated which resulted in return of the blood pressure to a normal range after surgical correction. It is suggested that many patients may be spared the painful, expensive, time-consuming, and sometimes dangerous procedures which are used in the detection and assessment of unilateral renal disorders. Photoscanning of the kidneys is a safe procedure which is external, nontraumatic, easily and rapidly performed. Several illustrative cases are reported.

Chemical Composition of Cell Walls of Streptococci

Hutton D. Slade,[5] Chicago, Illinois

Information on the chemical composition of the cell walls of streptococci is important for an understanding of the pathogenicity, virulence, and antigenicity of the microorganism. An analysis of purified cell walls from streptococcal groups A to Q by means of paper chromatography has been carried out.

All groups except O contain rhamnose. This result indicates that a fundamental chemical difference exists between the group O and the group A carbohydrate antigens. Rhamnose is an important constituent of the latter antigen. Also, O strains contain galactose, whereas A strains do not.

Differences among a few of the groups as to the presence of glucose and/or galactose have been found. E and A contain glucose only, and L contains galactose only. It is, of course, possible that a few exceptions to these generalizations may be found as more strains are examined.

Muramic acid occurs without exception in all strains, regardless of group. This result emphasizes the importance of muramic acid as a component of the cell-wall structure and the carbohydrate grouping antigen. In practically all cases, glucosamine and galactosamine are accompanied by glucose and galactose.

The amino acids present in largest quantity in streptococcal cell walls are alanine and glutamic acid. In some groups (C, G, L, N), lysine is present in trace quantities, whereas in the other groups lysine is a major component. Those amino acids possessing a variable distribution in trace quantities are aspartic acid, glycine, and serine.

These results indicate that the specificity of streptococcal grouping antigens depends primarily upon the stereochemical configuration of the complex rather than qualitative differences in composition.

Differentiation of Benign from Pathologic T-Wave Changes

Julian C. Sleeper, Walter L. Floyd, and Edward S. Orgain, Durham, North Carolina

Differentiation of benign from pathologic T-wave changes in the electrocardiogram remains difficult and empiric. In a search for possible distinguishing characteristics, 15 patients exhibiting benign T-wave changes in the absence of overt heart disease were studied with 12-lead electrocardiograms during or after the following: fasting, postprandially, deep inspiration, standing, hyper-

ventilation, exercise (fasting and postprandial), glucose ingestion, intravenous administration of 1 mg. atropine, 20 μg. epinephrine, and in 6 patients 20 mEq. KCl. The T waves were normalized in 12 and improved in the remaining 3. Benign T-wave changes, which were typically low in amplitude, diphasic or inverted, improved with fasting in 10, during deep inspiration in 5, following potassium in 2 (of 6), and less regularly following other procedures. The T-wave abnormalities were produced or accentuated by exercise in 10, epinephrine in 9, standing in 9, glucose in 8, and occasionally following other procedures. No procedure consistently normalized or improved the T-wave pattern; however, fasting combined with exercise and deep inspiration normalized the pattern in 10. In 6 patients with heart disease and ischemic T waves, exercise and standing accentuated the abnormalities. The other maneuvers caused insignificant changes. While these procedures will not, by themselves, completely separate benign from pathologic T-wave change, fasting, exercise, and deep inspiration are the most useful maneuvers in the differentiation.

Electrocardiogram in Acute Lead Intoxication in Children

Sheldon J. Slodki, Rene A. Arcilla, Benjamin M. Gasul, Harry Elam, and Joseph Greengard, Chicago, Illinois

The myocardial histopathologic findings reported in autopsy studies in man and in experimental acute lead intoxication in rabbits have suggested that possible related electrophysiologic abnormalities in man might also be found. Electrocardiograms were obtained in 71 cases of acute lead intoxication in children (aged 1 to 5 years) during the spring and summer "epidemic" which occurred in Chicago in 1960. Since rigid diagnostic criteria were exercised and the group studied was large, it is felt that our electrocardiographic findings are of significance. The most striking abnormalities found were similar to those reported in the experimental studies on rabbits, and our distribution curves demonstrate group tendency to prolongation of the QT_c, P-R interval and a leftward shift of the mean QRS axis. Evidence of chamber hypertrophy was found only in cases with severe clinical anemia, and it was felt to be unrelated to the myocardiotoxic effects of lead. Correlation with apparent clinical severity was more consistent than with the determined serum lead level. Abnormalities in rhythm were rare. It is felt that the myocardial effects of acute lead poisoning are not restricted to the extremely severe group, but occur in the milder cases as well and represent an unappreciated aspect of this disease.

Evaluation of the Vectorcardiogram Taken After Exercise in 164 Cases of Angina Pectoris

Arthur L. Smith, Sr., and Arthur L. Smith, Jr., Lincoln, Nebraska

In this series of 164 anginal patients, the accuracy of the electrocardiogram was 69.5 per cent (114 cases) while that of the vectorcardiogram was 89.5 per cent (147 cases). In no case was the vectorcardiogram negative when the electrocardiogram was positive. These patients were followed from 2 to 12 years; their ages varied from 29 to 69 years. No fixed exercise was given, but chest distress, dyspnea, or weakness was the required end point for recording. The cube electrode placements of Duchosal were used routinely and each loop was viewed on the oscilloscope for varying periods of time.

The vectorcardiograms were analyzed for changes in spatial orientation, configuration, conduction, and QRSsÊ-TsÊ angles. Rest values were used as controls to evaluate changes after exercise, and the criteria for diagnosis were derived from these. The greatest difference occurred in the T-wave rotation and the marked increase in its magnitude; in the QRS loop the configuration, the direction of the long diameter, and the inscription were the principal variations from the rest values. The change of greatest practical value was the increase in the spatial angle between the QRSsÊ and the TsÊ loops.

Since, in the United States, 30 to 50 per cent of anginal patients are negative reactors to all present tests, we believe it would be well to try the vectorcardiographic method of recording in these cases.

Catecholamines and Cardiac Excitability as Affected by Various Depths of Halothane, Ether, and Cyclopropane Anesthesia

S. L. Smith, W. R. Webb, L. W. Fabian, and V. D. Hagaman, Jackson, Mississippi

The purpose of this study has been to evaluate the effects of various depths of anesthesia by halothane, ether, and cyclopropane on the production of catecholamines and on cardiac excitability.

In 20 normal dogs, the heart was paced by a drive stimulus and strength-interval curves determined by a variable test stimulus. Studies were made throughout of the depth of anesthesia by using the standard electroencephalogram criteria, of the blood pressure, of arterial oxygen and CO_2 contents, hematocrit, epinephrine and norepinephrine levels, and pH.

Halothane, under these conditions, caused too great a blood-pressure fall to proceed past plane 1 of the third stage and lowered the hematocrit, while the other agents elevated the hematocrit.

Normal oxygen and CO_2 contents were maintained with all agents.

Halothane elevated norepinephrine minimally, and epinephrine only slightly. Cyclopropane stimulated norepinephrine slightly, but epinephrine minimally, while ether stimulated both in a crescendo-decrescendo manner as the level of anesthesia was deepened.

Ether caused only a slight elevation of the diastolic threshold, slowed the speed of conduction, and caused little or no change in the refractory period. Cyclopropane and halothane both lengthened the absolute refractory period and elevated the diastolic threshold, although halothane much more than cyclopropane. Cyclopropane affected the conduction minimally, while halothane slowed conduction approximately the same as ether.

The cardiac effects appear specific for the various anesthetic agents, as they do not follow the inotropic effects of the catecholamines or any of the other factors studied.

Estimation of Pulmonary Blood Flow Using Krypton-85

Harold Smulyan, Richard P. Cuddy, John F. Keighley, Charles R. Markason, and Robert H. Eich, Syracuse, New York

The technic of pulmonary blood flow (PBF) measurement using krypton-85 (Kr^{85}) was investigated in 16 anesthetized dogs. Kr^{85}, dissolved in saline, was infused into the right atrium at a constant rate; after 4 minutes for equilibration, simultaneous carotid artery (CA) and pulmonary artery (PA) samples were drawn and hemolyzed. These samples and known dilutions of infusate were counted in a jacketed Geiger-Müller tube and Kr^{85} PBF was calculated by the Fick principle. Indicator-dilution cardiac outputs (COP) were obtained by utilizing PA injections of indocyanine green and interrupted 1-second CA samples.

There was good agreement between 62 flows measured with Kr^{85}, each paired with a dye COP, during control periods and when hemodynamics were altered by hemorrhage, transfusion, morphine, atropine, and intermittent positive-pressure breathing. (Mean Kr^{85} PBF was 3.01, mean dye COP, 3.22 L./min.; $r = 0.96$; $y = 0.67 + 0.85X$; ±0.59 L./min.) These maneuvers provided a wide range of flows (0.46 to 9.59 L./min.) and changes from control levels in CA and PA blood Kr^{85} concentrations. Further changes in these concentrations induced by 6 balloon bronchial occlusions did not affect the PBF–dye COP agreement. This suggests that CA blood does approximate mixed venous Kr^{85} concentration. Reproducibility analysis of 82 pairs of Kr^{85} PBF's measured 3 minutes apart revealed: $r = 0.96$; $y = -0.04 + 1.05X$; ±0.5 L./min., but ±0.25 L./min. in the last 40 pairs.

The method is technically simple, reproducible, repeatable as often as samples can be drawn, and checks well with the dye COP during control and altered blood flow and Kr^{85} concentrations.

Excretion of Uric Acid After Thiazides in Man

William H. Soderstrom, Walter M. Kirkendall, Howard L. Nash, and Lewis J. Garrotto, Iowa City, Iowa

We designed these studies to learn if renal retention of uric acid (UA) was involved in the rise of serum UA commonly observed in persons taking thiazides.

The clearance of uric acid (C_{UA}) was studied in 4 controls and in 8 patients given hydrochlorothiazide intravenously following 3 control periods. One group was followed for 1½ hours after treatment, a second for 3½ hours. Standard methods were used for inulin, electrolyte, and water clearances.

Controls showed progressive UA retention, perhaps because of overnight fasting and acidosis. Four subjects studied for 1½ hours after hydrochlorothiazide had insignificant change in C_{UA} after the thiazide. Four subjects studied for 3½ hours had decreases in C_{UA} compared with controls ($P < 0.025$). There was no significant change in inulin clearance. C_{UA} showed the greatest fall after peak potassium clearance.

Two men were given a constant formula diet. After a 6-day control period, chlorothiazide, 500 mg. twice daily, was given for 5 days, followed by a 3-day postdrug period. Both subjects showed a decrease in creatinine clearance and C_{UA}. Serum UA and urinary excretion of sodium, potassium, and chloride rose. One subject who did not lose significant body weight retained 145 mg. of UA during therapy, while his serum UA rose 1.38 mg. per cent ($P < 0.005$). During the postdrug period, C_{UA} rose above control values.

With no initial change in glomerular filtration rate, our studies indicate that an early effect of thiazides is to cause UA retention by an alteration in renal tubular function. Later, diminished UA filtration may contribute to serum UA rise.

Comparative Study of the Antihypertensive Effects of Guanethidine and Bretylium Tosylate

Louis A. Soloff, Philadelphia, Pennsylvania

Guanethidine was given, in addition to chlorothiazide, to 17 hypertensive subjects who, for over 3 years, had been refractory to a basic antihypertensive regimen and to the prolonged use of ganglion-blocking drugs and bretylium tosylate.

Guanethidine produced, primarily, an orthostatic hypotensive effect similar in magnitude to that produced originally by bretylium tosylate. As with bretylium, this effect was due primarily to a drop in cardiac output. Unlike bretylium, in 10 of the 17 patients a slight, but definite, supine hypotensive effect was also produced. Also unlike bretylium, the orthostatic hypotensive effect took 1 to 5 minutes to disappear after the supine position was assumed. Four of the 17 failed to maintain the hypotensive effect after 4 to 6 months. Occasional escapes to hypertensive levels were seen in the others. One developed intractable diarrhea while refractory to a hypotensive effect of increasing doses of guanethidine. Four requested to be taken off the drug because of weakness, particularly of the legs, and/or because of mental obtundation. The other 7 maintained an orthostatic hypotensive effect for 6 months with little change in doses.

Conclusion: Guanethidine is superior to bretylium tosylate, primarily because of its smoother and more persistent effect. Like bretylium, however, it lowers blood pressure unphysiologically by lowering cardiac output. The intelligent and articulate patient recognizes the consequent effects of diminished peripheral arterial blood flow.

Effect of *d*-Thyroxin on Blood Cholesterol and Ischemic Heart Disease

Louis A. Soloff and William L. Winters, Jr., Philadelphia, Pennsylvania

Two to 12 mg. of *d*-thyroxin were given daily, for as long as 6 months, to 5 groups of patients to determine its effects on blood cholesterol and on the manifestations of ischemic heart disease.

1. In 1 patient with spontaneous myxedema, cholesterol was brought to normal without producing euthyroidism.

2. In 5 patients with angina pectoris refractory to I^{131}-induced hypothyroidism, cholesterol was reduced in all, but angina was unaffected in 4 and increased in 1.

3. In 7 patients euthyroid with angina pectoris, cholesterol was reduced in 4; angina was unaffected in 3, increased in 2; and myocardial infarction occurred in 1. One who developed increased angina subsequently reverted to the pretreatment clinical status while still on the drug.

4. Of 9 patients with asymptomatic ischemic cardiac disease, 1 developed a rash and administration of the drug was stopped. Of the other 8, cholesterol was reduced in 7, angina pectoris occurred in 3, cardiac failure in 1, and myocardial infarction in 1.

5. Of 4 hypercholesteremic persons without manifest heart disease, cholesterol was reduced in 3.

Conclusion: *d*-Thyroxin will reduce significantly the blood cholesterol in most persons, but will not reduce the incidence of, nor prevent the appearance of, angina pectoris, nor prevent the development of myocardial infarction. Its major value, if any, is to reduce hypercholesteremia in those who as yet do not have significant heart disease.

Intracavitary Electrocardiographic Study of Atrial Arrhythmias

Andrew P. Somlyo, Joseph Grayzel, and A. Gregory Jameson, New York, New York

The purpose of the present study was to determine the morphology of P waves associated with various ectopic atrial foci in order to identify the origin of ectopic rhythms associated with inverted P waves in lead I. Simultaneous intracavitary and surface electrocardiograms were obtained in patients undergoing right- and left-heart catheterization. An intracavitary electrode placed at the tip of a cardiac catheter was employed to produce atrial premature contractions, as well as to localize spontaneously occurring ectopic foci. This technic permits a study of the spread of excitation not obtainable from surface records. When excitation began in the left atrium, the P wave in lead I was inverted, exceedingly small, or isoelectric. Right-atrial foci did not produce inversion of the P waves in lead I. The P-R interval associated with left-atrial foci was either equal to or greater than the P-R interval occurring with normal sinus rhythm. These features of left-atrial foci were also seen to occur spontaneously in routine clinical electrocardiograms. It appears that left-atrial rhythms are detectable clinically and deserve further investigation.

Electrocardiographic Studies in Eighty-eight Cases of Tricuspid Atresia

Andrew P. Somlyo and Katherine H. Halloran, New York, New York

The electrocardiograms of 17 of our own patients with tricuspid atresia and 71 cases collected from the literature were studied to determine the frequency and significance of normal or right electrical axis evidence of left-ventricular hypertrophy in precordial leads, and the changes following palliative surgery. Twenty-nine patients had associated pulmonic atresia or transposition of the great vessels with large pulmonary arteries; 15 of these showed a normal axis or right-axis deviation. Of the remaining 59 cases, only 5 had a normal axis and none had right-axis deviation. Normal or right axis was not related to early infancy. Precordial leads generally revealed evi-

dence of left-ventricular predominance, but the criteria of left-ventricular hypertrophy were fulfilled in only 9 of our 17 patients. Following palliative shunt procedures, flat or inverted left-precordial T waves became upright and P-wave voltage decreased. An increased postoperative P-wave voltage appeared to be related to poor clinical response in 2 patients. Enlargement of the atrial septal defect in 1 was followed by clinical improvement and decrease in the height of the P wave. It is concluded that the presence of normal or right axis is helpful in the diagnosis of associated lesions in tricuspid atresia and is unrelated to age. P-wave changes following palliative surgery should be evaluated further as possible criteria for enlargement of the atrial septal defect.

Rheumatic Activity and Congestive Heart Failure in Young Patients with Rheumatic Heart Disease

Mario Spagnuolo and Alvan R. Feinstein, Irvington-on-Hudson, New York

In young patients with rheumatic heart disease, congestive heart failure is traditionally believed to be due to rheumatic activity and is said to lower the sedimentation rate (ESR). The present study has analyzed these and other features of 70 episodes of congestive heart failure in 32 patients, aged 4 to 18 years, with rheumatic heart disease.

On purely clinical grounds, the congestive heart failure was classified into 2 groups. "Active" congestive heart failure was associated with joint symptoms, or pericarditis, or occurred as a "rebound" within 5 weeks after cessation of anti-inflammatory therapy in a presumably active patient. "Inactive" congestive heart failure lacked the above features and was associated with insufficient cardiotonic therapy, excess physical exertion, infection, or pulmonary infarction. The analysis of data showed that the "active" and "inactive" groups had no essential differences in age or in clinical manifestations of congestive heart failure. In both groups, dyspnea was the most frequent single symptom but was often absent; pulmonary signs were seldom present. Hepatomegaly was the most common single sign and hepatic tenderness was a useful early diagnostic clue. Facial edema, often reported in previous studies, was not found.

The ESR and serum C-reactive protein (CRP) were abnormally high in all 26 "active" episodes, except in 5 which were under anti-inflammatory treatment. Evidence of group A streptococcal infection was found only in "active" patients. Six of the 8 infection-infarction episodes had high ESR and all had high CRP's. By contrast, the 46 noninflammatory "inactive" episodes were normal for ESR in 33 and CRP in 25.

These data show that congestive heart failure does *not* lower an inflammatorily elevated ESR and that congestive heart failure can occur without rheumatic activity in young patients as well as in adults. The absence of rheumatic activity can be suspected clinically and confirmed by a normal ESR or CRP.

Possible Anatomic Basis for Sudden and Unexpected Death in Individuals with Advanced Coronary Atherosclerosis (P)

David M. Spain, Brooklyn, New York, Victoria A. Bradess, Pedro T. Iral, and Antonia G. Cruz, Valhalla, New York

In order to gain further insight into the reasons for sudden and unexpected death from coronary atherosclerosis in apparently "healthy" males, over 125 hearts in males between the ages of 35 and 55 were studied as follows:

The ostia of both main coronary arteries were cannulated. Under a constant pressure of 70 to 75 mm. Hg, the left main coronary artery was perfused with physiologic saline until fluid flowed freely from the right ostium. Special plastic beads 40 to 75 μ in diameter were then introduced into the left ostium and the fluid obtained from the right ostium was examined for the presence of these beads. The coronary arteries were then injected with barium-gelatin and x-rayed. The vessels were studied for the degree of coronary atherosclerosis and occlusion, and the myocardium for evidence of infarcts. The cases were divided into 3 groups: those with minimal to moderate atherosclerosis who had died as a result of accident; those with advanced coronary atherosclerosis and no infarcts who had died suddenly and unexpectedly; and those with advanced coronary atherosclerosis and myocardial infarcts.

Intercoronary anastomoses of sufficient caliber to permit passage of 40- to 75-μ beads under 75 mm. Hg pressure were present only in those individuals with myocardial infarcts. The degree of coronary atherosclerosis and luminal narrowing bore no relationship to the passage of the beads. Those individuals who died suddenly with advanced coronary atherosclerosis in the absence of myocardial infarction revealed no evidence of intercoronary anastomosis according to the technic of this study, and may be a possible anatomic basis for sudden and unexpected death.

Simple Computer Technic for Monitoring Cardiac Output and Peripheral Resistance

Merrill P. Spencer, Haruka Okino, and Richard L. Berry, Winston-Salem, North Carolina*

A new combination of physiologic and computer technics makes possible this continuous measurement using the aortic pressure (P). A single lumen catheter with a lateral pressure port near its tip is passed via the femoral artery to the descending thoracic aorta. While the pressure-pulse contour is monitored, the tip is positioned at the nodal point where the resonant pressure waves are minimal. The pressure recorded here (approximately 10 cm. below the left subclavian artery) agrees with that expected in a simple "windkessel." The computation is performed by feeding a signal representing P into an augmenting differentiator which solves the windkessel equation

$$F = C\frac{dP}{dt} + \frac{1}{R}P.$$

(F) is the input flow from the left ventricle, (C) is the compliance of the arterial tree, and (R) is the total peripheral resistance. (C) is set at any convenient value, while the amount of augmentation, $\frac{1}{R}$, is adjusted until the (F) contour is flat (like the actual F from the left ventricle) throughout diastole. (R), thus determined, represents the peripheral resistance, while $\frac{1}{R}P$ is the peripheral flow. Calibration in ml./min. may be performed by a simultaneous determination with the indicator-dilution or Fick method. Without calibration, the method, in a given individual, gives relative changes useful in many surgical and medical procedures. Variations in (C) do not affect the mean peripheral flow.

Contraction of Potassium-Depolarized Frog Ventricular Strips by Electric Current

Nick Sperelakis, Cleveland, Ohio

Potassium-depolarized visceral smooth muscle strips generate tension in electric fields. Hence, potassium-depolarized ventricular strips of the frog heart were subjected to electric fields. The field strengths necessary to generate equal tensions were much higher in depolarized muscle (5 to 20 volts/cm.) than in nondepolarized muscle (0.5 to 2 volts/cm.). The field-induced contractions of depolarized strips were much slower than the contractions of normally polarized strips. Maximal tension varied directly, within limits, with strength and duration of the field. Longitudinal and transverse fields were about equally effective. Tensions generated in sinusoidal A.C. fields fell off markedly between 50 and 1,000 c.p.s.; the low tensions generated at the higher frequencies could be increased by larger field strengths. Acetylcholine and epinephrine, in doses up to 50 μg./ml., had no effect upon the field-induced contraction. The muscles were perfectly recoverable, and spontaneous contractions often returned shortly after repolarization in Ringer's solution. Potassium-depolarized frog sartorius muscle and cat papillary muscle, however, did not respond to electric fields. The results suggest that vertebrate muscles which are not highly striated may be experimentally activated by electric current independent of action potentials.

The Diagnostic and Prognostic Category, Suspect Coronary Heart Disease

Jeremiah Stamler, Howard A. Lindberg, and David M. Berkson, Chicago, Illinois

A key problem confronting clinical investigation today is the diagnosis of disease in its early, incipient, or suspect stages. This is particularly important when incidence and mortality from frank disease are high and when recent research advances offer the possibility of primary and secondary prevention. These conditions prevail conspicuously today with respect to atherosclerotic coronary heart disease (CHD). The present study, begun on January 1, 1958, involves the long-term follow-up of 1,594 men aged 40 to 59 years, the entire male labor force of this age employed by a Chicago utility company. Definite CHD was found in 43 per 1,000 men (age-corrected rate). The category, suspect CHD, was used to designate men with suspect (but not definite) angina pectoris, with suspect (but not proved) episodes of myocardial infarction or coronary insufficiency, with certain electrocardiographic abnormalities not pathognomonic of definite CHD. Men with suspect CHD have a 2- to 3-fold greater risk of developing frank CHD in middle age than men free of any clinical signs of CHD. The overall prevalence rate of suspect CHD was 122 per 1,000. The prevalence rate of suspect CHD was significantly higher in hypercholesterolemic than in normocholesterolemic, hypertensive than normotensive, obese than nonobese men. In men with combinations of these abnormalities, suspect CHD prevalence rate was 4- to 8-fold greater than in normal men. These findings lend support to the concept that suspect CHD is a valid diagnostic and prognostic category. It would seem advisable in men with suspect CHD to institute prompt measures in an attempt to correct risk-increasing abnormalities and to achieve possible prevention of frank CHD.

Five Years' Experience of the Rheumatic Fever Registry, Heart Disease Control Program, Chicago Board of Health

Jeremiah Stamler, John R. McDonough, and Harry C. Gibson, Chicago, Illinois

In 1956, the Heart Disease Control Program, Chicago Board of Health, in cooperation with several agencies, initiated a Rheumatic Fever Registry for the secondary prophylaxis of rheumatic fever—rheumatic heart disease. This Registry has since undergone steady growth, so that by December 31, 1960 it included 5,149 clinic and private patients, roughly estimated to approximate about 50 per cent of cases in children and young adults in Chicago. Of this total, 3,454 received free prophylactic drugs from the Registry, on prescriptions from their physicians. Oral sulfadiazine, oral penicillin, and injectable penicillin have been made available. An effort is made to ascertain and enhance diagnostic accuracy by requiring description of manifestations (modified Jones's criteria). Of the cases registered, all but 231 were reported to have 1 or more major manifestations, with or without rheumatic heart disease. An IBM data-processing system has been used to record the distribution of drugs and to verify keeping of appointments. Failure to keep appointments initiates a follow-up procedure, with the physician's cooperation, including a home nurse visit, if necessary. Recurrence rate of reported acute rheumatic fever in registered cases is estimated to be about 10/1,000/year. In contrast with these few recurrences, about 150 recurrences per year have been reported to the Board of Health in nonregistered cases. The experience of these five years is evaluated as demonstrating the feasibility and worth of a Rheumatic Fever Registry in a metropolis.

Congenital Aortic Stenosis and Pseudocoarctation of the Arch of the Aorta

Israel Steinberg and Jack W. C. Hagstrom, New York, New York

Pseudocoaretation is an uncommon congenital anomaly of the arch of the aorta which is embryologically and anatomically similar to coarctation except that there is no aortic occlusion. Consequently, hemodynamic abnormalities do not occur, and the arm and leg blood pressures are normal and equal; collateral circulation does not develop. In the conventional roentgenogram, there is a double rounded shadow along the left superior mediastinum. The upper mass may be mistaken for a mediastinal tumor or aneurysm; the lower one may be interpreted as the aortic knob. Angiocardiography, however, readily delineates the unusually dilated and deformed arch of the aorta and demonstrates that the lower shadow is really the dilated ("poststenotic") descending aorta.

Heretofore, except for 2 patients with aneurysmal dilatation of the aortic sinuses, associated anomalies of the aorta have not been reported in pseudocoarctation. In 4 patients with congenital aortic stenosis and pseudocoarctation, 2 had bicuspid aortic valves. The first, in a 12-year-old boy, was encountered at operation for aortic stenosis; the other case was found at post mortem in an adult who died of heart failure owing to parietal endocardial fibrosis and fibroelastosis. Because 1 previously reported patient with pseudocoarctation developed bacterial endocarditis on the aortic valve, patients with pseudocoarctation, as in other types of congenital cardiovascular defects, should have antibiotic or chemical prophylactic therapy whenever dental or surgical procedures are contemplated.

Angiocardiography in Diagnosis of Cor Pulmonale and Pericardial Effusion in Scleroderma

Israel Steinberg and Sidney Rothbard, New York, New York

Two women, in their fourth decades, with generalized scleroderma, right-axis deviation, and right-ventricular hypertrophy in the electrocardiogram had severe heart failure. Both had markedly enlarged, albeit feebly pulsating, cardiac silhouettes. Angiocardiography revealed pericardial effusions, dilatation of the right atria, ventricles, and pulmonary arteries, with marked delay in passage of contrast material through the cardiovascular system. Despite digitalization, mercurial diuretics, and pericardiocenteses, relentless progress to death ensued in the first patient. At post mortem, the heart was enlarged, but only the right atrium, ventricle, and pulmonary artery were dilated; the right-ventricular myocardial wall was hypertrophied and the myocardium showed only minimal fibrosis. The pericardium contained hemorrhagic fluid and showed focal fibrosis. The lungs were emphysematous, while the pulmonary arteries and arterioles were arteriosclerotic with narrowed lumina. Noteworthy were intimal proliferation, subendothelial fibroplasia, thickening of the adventitia, and reduplication and fragmentation of the intima of the pulmonary arterial vessels. The second patient improved after digitalis, diuretic, and corticosteroid therapy, although the huge cardiac silhouette was unaltered.

Angiocardiography is recommended for diagnosis of the type of heart disease, whether right- or left-sided, in patients with scleroderma who have enlarged cardiac silhouettes. Pericardial effusion, cor pulmonale, or left-sided heart disease will thus be revealed and facilitate the appropriate treatment, such as pericardiocentesis and, of course, digitalization and diuretic therapy.

Experimental Coronary-Artery Occlusions Secondary to Atherogenic Diets

Sam E. Stephenson, Jr., Rachel Younger, and H. William Scott, Jr., Nashville, Tennessee

The production of experimental atherogenesis in recent years has been undertaken not only to evaluate the naturally occurring factors that lead to its production, but also to evaluate methods of surgical therapy for arterial occlusive disease. For the last 4 years, it has been possible in our laboratory to produce experimental atherogenesis in the dog by the utilization of a high-cholesterol diet and toxic doses of vitamin D in combination. These studies have demonstrated a high incidence of satisfactory preparations occurring in from 3 to 8 months of treatment.

Recent work by Sabiston et al. has shown the production of experimental coronary arteriosclerosis by producing a hypertensive system in the coronary arteries by coarctation of the ascending aorta. This is not a normally occurring hemodynamic system, and because of this we have attempted to develop arteriosclerotic plaques in the coronary arteries of normotensive dogs. Of 18 animals, 16 have shown marked arteriosclerotic lesions advancing to total occlusion of main and branch coronary arteries.

Illustrative photographs and photomicrographs of the experimental preparations and details of the experimental procedure employed are presented.

Pulmonary Origin of the Left Coronary Artery: A Therapeutic Dilemma (P)

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The currently proposed therapeutic ligation of the aberrant left coronary artery arising from the pulmonary artery necessitates a careful evaluation of the functional disturbance produced by this lesion. The physiologic handicap of the aberrant left-coronary origin is related to the lower perfusion pressure of the lesser circulation. Intercoronary communications are of benefit to left-ventricular perfusion in allowing a shunt into the left-coronary-artery system from the right coronary artery receiving blood at aortic pressure and saturation. In addition, these intercoronary communications may lead to flow from the left coronary artery into the pulmonary artery. However, this so-called "myocardial bypass" is functionally unimportant.

Clinical and angiocardiographic support for this stand is as follows: (1) prolonged survival following poudrage without left-coronary-artery ligation; (2) contrast-study evidence of patients having pulmonary-artery to aberrant left-coronary-artery flow; (3) contrast-study evidence of right-coronary-artery to aberrant left-coronary-artery flow in an older child whose survival and electrocardiogram reflect the benefits of the intercoronary communications; (4) absence of myocardial changes in patients whose left-coronary-artery fistulas allow communication with and dissipation into low-pressure sites; and (5) prolonged survival of patients with aberrant right-coronary-artery origin.

Therapeutic efforts should be made toward improving left-ventricular blood supply through pericardial abrasion and, when feasible, left-coronary-artery transplantation from the pulmonary artery to a systemic artery. Ligation of the aberrant vessel is detrimental when the blood supply originates from the pulmonary artery. It furthermore precludes a systemic anastomosis.

Observations on Lipid and Other Parameters During Cholesterol Control

Merritt H. Stiles, Gilbert B. Manning, and George Stewart, Spokane, Washington

Studies were made of levels of protein-bound (PBFA) and free (FFA) fatty acids, phospholipids (PL), triglycerides (Tg), total (CH) and esterified (CE) cholesterol, protein-bound iodine (PBI), and various carbohydrate parameters in normocholesterolemic and hypercholesterolemic subjects, and in hypercholesterolemic individuals undergoing dietary, thyroid (T), and triparanol (MER) therapy. Urinary levels of vanilmandelic acid (VMA) were studied, and gas chromatographic analyses were made of CE, PL, and Tg.

VMA levels, studied in the hope that they might reflect stress factors, demonstrated no clear-cut correlation with cholesterol levels in the individuals studied. There was a correlation between CH and PBI, although with much individual variation. The correlation was best illustrated in serial studies of individuals on thyroid therapy.

Cholesterol levels fell in persons placed on diets in which saturated fats were largely replaced by polyunsaturated fats (CLB), and in individuals on MER and on T. The response to MER was inconsistent. More consistent lowering of the cholesterol level was seen when T was given, particularly when the PBI was raised above 6 μg. per cent. The greatest lowering was seen when CLB, T, and MER were combined. Graphs have been made illustrating the changes discussed. Other suggestive, but not well-defined, correlations have been noted. Changes in PL, PBFA, FFA, and Tg, and variations in the fatty-acid composition of CE, PL, and Tg, as determined by gas chromatography, were also noted. Unexpectedly high percentages of low-molecular-weight, short-chain fatty acids were encountered in some instances, particularly in individuals undergoing thyroid therapy.

Importance of Duration of Ventricular Fibrillation and Effect of Intracardiac Drugs upon Survival in Dogs Following External Massage and Defibrillation

Harry Stoeckle, John C. Schuder, and Hugh E. Stephenson, Jr., Columbia, Missouri

Mongrel dogs anesthetized with intravenous pentobarbital sodium were made to fibrillate by means of a single fibrillatory shock. After an initial period of ventricular fibrillation, external cardiac massage was initiated and continued until a single or double external defibrillatory shock was applied.

Fifty-one dogs were employed in the first series which was designed to familiarize us with the pattern of the physiologic response in regard to cessation of respiration, dilation of the pupils, relationship between the force of the initial chest compressions and the frequency of fracture of the ribs and rupture of the liver, and the amplitude and rate of fibrillation with respect to both the duration of unassisted fibrillation and the duration of effective cardiac massage.

The second series consisted of groups of 10 dogs each in which unassisted fibrillation was permitted for 4, 6, 8, and 10 minutes before external massage was initiated. A 5-minute period of massage was followed by a defibrillatory double shock. The number of long-term survivals was 7, 4, 4, and 1 for the respective groups.

The third series consisted of groups of 10 dogs each in which various emergency-type drugs were administered (intracardiac) at the end of 10 minutes of unassisted fibrillation. After 2 to 5 minutes of external massage, a defibrillatory double shock was applied. There were 6 long-term survivors in the epinephrine group, 1 in the procaine amide hydrochloride group, and none in the *l*-norepinephrine group.

Successful defibrillation was seemingly correlated with our ability to achieve a relatively high amplitude and rate of fibrillation potential at the end of the massage period.

Effects of Graded Doses of Norepinephrine on Arterial Blood Pressure in Patients with Diabetic Neuropathy and Orthostatic Hypotension

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Diabetic patients with neuropathy may have orthostatic hypotension and diminished responsiveness to stimuli mediated over efferent sympathetic pathways. Extensive postganglionic sympathectomy may produce similar changes. Both postganglionic denervation in man and reserpine-induced catecholamine depletion in animals cause vascular hyperresponsiveness to exogenous norepinephrine. These facts suggested that diabetics with neuropathy and orthostatic hypotension might show exaggerated pressor responses to norepinephrine infusions.

Pressor responses to graded doses of norepinephrine were measured in 12 men. Six were normal. Six had diabetic neuropathy with orthostatic hypotension. None had hypertension or occlusive vascular disease. Norepinephrine base was infused intravenously at 0.05, 0.1, and 0.2 μg./Kg./min. for 4 minutes. Each subject received each dose twice. The sequence of infusions was randomized in both control and diabetic groups using the same 6 by 6 Latin Square. Pulse rate and arterial pressure (cuff) were measured at 1-minute intervals before and during infusions.

Dose-response regressions were computed using a logarithm of the norepinephrine dose. The blood pressure responses were significantly greater in diabetics. Analysis of variance of the data indicated the validity of a parallel line assay. The relative potency of norepinephrine in diabetics with respect to controls was 3.0 and with 95 per cent fiducial limits of 2.6 and 3.8. The decrease in heart rate with norepinephrine was significantly less in the diabetics than in the controls.

Conclusion: Diabetics with orthostatic hypotension had exaggerated pressor responses to norepinephrine. This is consistent with the hypothesis that diabetic neuropathy resembles postganglionic sympathetic denervation.

Effects of Changing Plasma and Erythrocyte Lipids, In Vivo, on Blood Gases and Arterial pH

Leonard J. Stutman and Menard M. Gertler, New York, New York

Previous experience with lipemia has shown that there is a drop in oxygen saturation of erythrocytes during lipemia. This phenomenon has been thought to be related to the level of neutral fat in the plasma. In addition, other investigations have shown changes in myocardial oxygen uptake and myocardial blood flow.

In these studies, an attempt has been made to determine whether there is any direct effect of lipids on the red cell itself which may affect oxygen and carbon-dioxide transport. Dogs were given intravenous fat infusions (2 Gm./Kg.) under standard conditions. Whole-red-blood-cell lipids and plasma lipids were determined, as well as arterial pH, pO_2, pCO_2, O_2 saturation, O_2 capacity, and CO_2 capacity. With a rise in the plasma lipids, there was a rise in the whole-red-blood-cell neutral fat, phospholipids, and nonesterified fatty acids (NEFA). There was a drop in arterial pH of 0.11 unit, in O_2 saturation of 2.36 volumes per cent, and in erythrocyte oxygen content of 4.12 volumes per cent (12.6 per

cent drop). Concomitantly, there was no significant change in the CO_2 content of the erythrocyte. The plasma pO_2 dropped 17.3 mm. (31 per cent). The plasma pCO_2 dropped 6.2 mm. (18 per cent).

Of special interest is the rise in erythrocyte NEFA which not only confirms previous in vitro evidence of red blood cell–fatty acid interaction, but supports the concept of the role of the red blood cell in fat transport.

In conclusion, high levels of infused lipid coat erythrocytes and interfere with oxygen and carbon-dioxide transport both in the plasma and in the red blood cell.

Alterations in Blood Sodium as Measured by a Glass Electrode (P)

Kenneth Sugioka, Thomas C. Gibson, and Mary Hinternhoff, Chapel Hill, North Carolina

The continuous and accurate measurement of blood-sodium levels is now possible by the development of a sodium ion-sensitive glass electrode which can be used in the intact living animal.

An artificial arteriovenous shunt was created by cannulating the femoral artery and passing the blood through a cuvette and back into the femoral vein of the animal. The glass and reference electrodes were mounted in the cuvette and their electrical output was amplified and recorded on a direct-writer. Sodium-ion concentrations in milliequivalents, as measured by the glass electrode, were found to be in close agreement with values as determined by simultaneous flame-photometer measurements. With the cuvette in place, the animals were made hyper- or hyponatremic by the rapid infusion of either 5 per cent sodium chloride or 5 per cent dextrose in water. A continuous lead II electrocardiogram was taken simultaneously to correlate changes in blood sodium with electrocardiographic changes. Reduction of blood sodium to 75 per cent of control levels produced no changes other than a slowing of heart rate. Increase of blood sodium to levels of 40 per cent above the control reading gave rise to increase in rate, decrease in voltage, and T-wave flattening and inversion.

The sodium electrode has proved an accurate, useful tool in continuously measuring concentrations of sodium ions in the blood of the intact animal. Minor electrocardiographic changes occurred when blood-sodium levels were elevated at least 40 per cent above the control reading. In this study, the average control level was 144 mEq. per cent.

Pressure Gradients and Peripheral Resistance in Systemic Circulation (P)

Takero Sugiura and Edward D. Freis, Washington, District of Columbia

Measurement of blood pressure in the small vessels of the hamster cheek pouch, using the direct-micropuncture (Landis) technic, demontrated a pressure drop of 57 per cent between the carotid and cheek-pouch arteries of 150 μ. By contrast, the pressure drop from the small arteries to the small veins represented only 26 per cent of the mean carotid pressure.

Subsequent studies have been carried out using the mesentery of the guinea pig, where small arteries up to 550-μ diameter are available for micropuncture. During Inactin anesthesia, pressures were measured in the carotid artery first by direct micropuncture and then by strain-gage recording after cannulation with polyethylene tubing. In 13 animals, the mean carotid pressure averaged 63 $\pm$ 6 mm. Hg by both methods.

The mesentery then was exposed under mineral oil and micropuncture of the small arteries carried out. Carotid pressure was monitored with a strain gage. Results were discarded in animals exhibiting a significant fall of carotid pressure. In 25 animals, mean pressures in the mesenteric arteries averaged as follows: 45 $\pm$ 5 mm. Hg in vessels of approximately 500-μ diameter; 43 $\pm$ 5 mm. Hg in 400-μ arteries; 36 $\pm$ 6 in 300-μ, and 32 $\pm$ 6 in 200-μ vessels. Mean carotid pressure in the same animals averaged 63 $\pm$ 9 mm. Hg. Thus, the pressure fall from the carotid to mesenteric arteries of 500-μ diameter averaged 29 per cent, increasing to 32, 43, and 49 per cent, respectively, as the arterial diameter decreased to 400, 300, and 200 μ, respectively.

Pressure drops of similar magnitude have been predicted to occur in small arteries by applying Poiseuille's law, but are at variance with popular opinion that the systemic peripheral resistance is confined primarily to arterioles.

Myocardial Metabolism in Muscular Dystrophy (P)

John F. Sundermeyer, Sigmundur Gudbjarnason, Vernon E. Wendt, Pancras B. den Bakker, and Richard J. Bing, Detroit, Michigan

Muscular dystrophy involves cardiac as well as skeletal muscle. Cardiac metabolism was studied in 11 muscular dystrophy patients (10 Duchenne type and 1 facioscapulohumeral type) by means of coronary sinus catheterization. Arterial and coronary venous bloods were analyzed for oxygen, glucose, pyruvate, lactate, inorganic phosphate, and aldolase. Coronary blood flow was determined in several patients at rest and on exercise. Glucose was extracted by the heart in all patients; pyruvate was utilized in 7 and released in 2. Lactate was extracted by the heart in all but 1 patient, in whom it was released. Myocardial blood aldolase balances were negative in 3 patients. The significant find-

ings were elevated inorganic-phosphate blood levels in all patients. In addition, as the arteriovenous redox potential differences between arterial and coronary venous blood became negative (the result of increased ratio lactate/pyruvate in coronary venous blood), the myocardial extraction of glucose increased. This suggests glycolysis. The oxygen extraction ratios of glucose were less than 100 per cent in all cases, showing oxidative breakdown of substrates other than glucose in the presence of glycolysis. A linear relationship between myocardial glucose extractions and inorganic-phosphate levels in the blood was demonstrated. It is concluded that an uncoupling of oxidative phosphorylation may occur in the myocardium in muscular dystrophy. As a result, glycolysis represents the main source of energy.

Ventricular Ectopic Beats with Fixed and Varying Coupling: Incidence, Clinical Significance, and a Comment on Mechanism

Borys Surawicz and Murdo G. MacDonald, Burlington, Vermont

Multiple ventricular ectopic beats (EB) were analyzed in long strips of 1 electrocardiographic lead in 104 consecutive patients and life insurance applicants. Thirty persons had severe heart disease, 17 moderate, 19 mild or questionable, and 38 no heart disease. Twenty-eight patients received digitalis.

Duration of coupling interval (CI) of each EB was correlated with the preceding R-R interval and the interval between the preceding and the examined EB (IEI). Coupling was fixed within 0.08 second in 30 persons with varying heart rate and in 8 persons with rate fixed within 0.10 second. Coupling was variable in 57 persons with varying and in 9 with fixed heart rate. Of 66 persons with variable coupling, 52 had either fusion beats or EB between end of U wave and P wave.

There was no significant difference in the incidence of any type of EB in any case category. Of 6 patients who died suddenly within 5 days after study, 5 had varying and 1 had fixed coupling.

It was postulated that variations in CI were usually determined by the functional state of the area of formation of the ectopic impulse and not the state of the whole ventricular myocardium because: (1) variations in CI frequently occurred without a constant common multiplicant of IEI; (2) in the presence of a constant common multiplicant of IEI, an "exit" block had to be postulated on occasions in each case; and (3) in 17 persons without a constant IEI, an inverse relation between the duration of CI and the preceding R-R interval was observed.

Significance of Body Position on Intrapleural and Esophageal Pressure and in Ventilatory Mechanisms

Edgar L. Surprenant and Simon Rodbard, Buffalo, New York

We have re-examined the effects of body position on certain aspects of ventilatory–pulmonary vascular mechanics. Catheters in the intrapleural space of dogs show that assumption of the upright position results in an intrapleural difference from diaphragm to apex of as much as 15 mm. Hg, a value approximately equal to the difference in height between the points of measurement. Pressures obtained with small balloons placed at various levels of the esophagus in man and in the dog vary in the same direction as the intrapleural pressures. The significant differences in intrapleural pressure from apex to base must be considered to affect the pulmonary veins which course primarily between the pleural walls. Further, the differences in intrapulmonary air pressure in these segments must affect the transpulmonary pressures in some manner which can be balanced only by similar variations in intrapulmonary air pressure. The intrapleural hydrostatic effects in the regulation of pulmonary blood flow and air exchange are discussed.

Relationship of Pressure and Flow in Perfused Pulmonary Artery Wedge Segments in Man

Harold J. C. Swan, Guy R. Dumont, and Arthur H. Kitchin, Rochester, Minnesota

If a cardiac catheter is wedged in the peripheral lung field, perfusion of the segment so isolated from the remainder of the lung may be done readily. If one knows the pressure gradient across the catheter and the downstream pressure (static wedge or left atrial pressure), the pressure gradient (ΔP) across this segment of small pulmonary vessels may be computed for any predetermined constant flow rate (Q). In dogs, reproducible pressure-flow curves with infusion of saline, dextran, and blood can be obtained in certain segments without vascular damage. Furthermore, the $\Delta P/Q$ relationship may be changed by many maneuvers.

Similar perfusions using saline, dextran, and patients' arterial blood were done in 30 humans with and without pulmonary vascular disease. A hysteresis loop usually was inscribed when Q was increased and then decreased in stepwise fashion. The data were generally reproducible within segments and demonstrated the expected relationship of a greater $\Delta P/Q$ in patients with pulmonary vascular disease than in those without. Within the former group, however, no relationship between pulmonary vascular resistance and $\Delta P/Q$ was demonstrated, and the considerable variation

between segments and between lobes was considered evidence of the patchy nature of the pulmonary changes. In 8 high-resistance segments, infusion of (relatively) large amounts of acetylcholine either had no effect or further increased the $\Delta P/Q$ ratio.

Such perfusion of isolated segments in vivo permits study of certain mechanical and reactive properties of the lung. A wide difference in "resistance" was found between different segments of lungs with vascular disease. A vasomotor response has not been demonstrated in such segments.

Diagnosis and Surgical Treatment of Chronic (Healed) Dissecting Aneurysm of the Thoracic Aorta (P)

Rodman E. Taber and Conrad R. Lam, Detroit, Michigan

This presentation concerns the diagnosis and successful surgical treatment of chronic or "healed" dissecting aneurysm of the thoracic aorta in 3 patients. Symptoms and radiographic evidence of aneurysm formation were present for many months or years. The symptoms of intra-abdominal dissection are frequently interpreted as representing gastrointestinal disease. Angiocardiography demonstrated findings considered characteristic of this condition. Surgical treatment consisted of resection of the descending thoracic aorta from the left subclavian artery to the level of the diaphragm and replacement by a Dacron prosthesis. In the course of restoring aortic circulation, the distal, double-barrel aortic channel was converted into a single aortic pathway to arrest further dissection. A partial bypass from the left atrium to the femoral artery was used to protect the spinal cord during the operative procedure. The intramural dissection began with an intimal tear in the proximal descending aorta and extended into the upper abdomen in each case. Although a site of re-entry for spontaneous internal decompression was not visualized in these patients, this interesting pathologic feature has been demonstrated as one of the mechanisms responsible for "arrested dissection." Other features have also been identified which may lead to a chronic dissecting aneurysm. Cystic medionecrosis was found to be the underlying pathologic condition which led to the dissection. None of the patients demonstrated the clinical findings of Marfan's syndrome.

Influence of Whiskey on Oral Fat-Tolerance Curves

G. Douglas Talbott, John R. Keys, Bessie Keating, and Ann Carr, Dayton, Ohio

Hyperlipidemia is recognized as an undesirable metabolic state, particularly as it relates to atherosclerosis. It is important to recognize environmental habits which contribute to this condition. The purpose of this project was to study the influence of ingested alcohol on oral fat-tolerance curves. Twenty-five prisoners were placed in isolation for 1 week on a nutritionally analyzed diet. At the end of the first week, they ingested a fat formula, and blood samples were obtained for the entire lipid spectrum analysis at 0, 2, 4, and 6 hours. This analysis included cholesterol, cholesterol esters, phospholipids, phospholipid esters, total lipids, lipid protein fractions, total esterified fatty acids, triglycerides, and athero index. Returned to isolation for another week, the prisoners served as their own controls. They were again given a fat formula preceded by 6 ounces of bourbon whiskey, ingested over a 90-minute period. Blood samples at the same time increments were again obtained for lipid analysis. Statistical evaluations of the results were performed. These demonstrated the lipid fractions to rise significantly with the ingestion of the fat formula, and an even greater significant rise after whiskey ingestion. A third group of prisoners was given just whiskey without formula. Statistical evaluation of their fat-tolerance curves demonstrated no significant rise. Blood coagulations were performed in all 3 groups and no statistical difference could be demonstrated. There is clinical implication in this report, particularly as it relates to the American custom of the cocktail, hors d'oeuvres, and high-fat meals following ingestion of liquor.

Potassium Metabolism During Diuretic Therapy

Peter J. Talso, Chicago, Illinois, Alexander P. Remenchick, Hines, Illinois, Charles E. Miller, Lemont, Illinois, and Edward O. Willoughby, Hines, Illinois

The introduction of thiazide derivatives for mobilizing edema fluid and for treating high blood pressure has represented an important advance in the management of cardiovascular disease. With minor variations, these compounds are characterized by their diuretic potency, their hypotensive effect, and their relative freedom from side effects. Of the side effects observed, the commonest and potentially most dangerous is hypokalemia. This investigation was designed to study the effect of thiazide derivatives upon potassium metabolism during the course of treatment of hypertensive cardiovascular disease.

Total body content of potassium was estimated by isotopic-dilution technics and simultaneously in some patients by the measurement of the body content of potassium-40. Serial studies in 120 patients have revealed that therapy with chlorothiazide, hydrochlorothiazide, benzydroflumethiazide, and polythiazide produced lowering of serum po-

tassium without change in total body potassium. Supplements of sodium or potassium chloride modified the hypokalemia induced by hydrochlorothiazide, but did not eliminate it. Ammonium chloride prevented the hypokalemia induced by hydrochlorothiazide, apparently by preventing alkalosis. Dichlorphenamide in conjunction with hydrochlorothiazide prevented alkalosis, but was accompanied by hypokalemia and significant depletion of total body potassium.

These studies demonstrate that therapy with thiazide derivatives is followed by an initial transient kaliuresis. Later, during prolonged therapy, hypokalemia is related to alkalosis and significant depletion of total body K does not occur unless additional factors supervene.

Effect of Pressor Amines on Indicator-Dilution Curves in Dogs with Experimental Intracardiac Shunts or Valvular Regurgitation

Herbert L. Tanenbaum, Washington, District of Columbia, and William Pfaff, Palo Alto, California

Indicator arterial dilution curves recorded following peripheral-vein or right-heart injections are helpful in detecting the presence of left-to-right cardiovascular shunts and valvular regurgitation. The interpretation of the dilution curve is often difficult in the presence of minimal shunting or regurgitation. This study is concerned with the alteration in dye-dilution curves following the administration of pressor amines to dogs with experimental shunts or valvular insufficiency. The diagnostic characteristics of such curves are exaggerated by temporarily increasing the hemodynamic abnormality.

Atrial and ventricular septal defects were created in 6 dogs each, mitral insufficiency in 5, and subclavian–pulmonary-artery anastomoses in 3 dogs. Systemic, pulmonary-artery, and atrial pressures were recorded with strain-gage transducers. Indicator-dilution curves were recorded from the femoral artery by using a cuvette densitometer and a direct-writing recorder. Systemic pressure and shunt flow were varied by an infusion of either *l*-norepinephrine or methoxamine hydrochloride. Alteration of the curves suggested an increase in left-to-right shunting in all of the animals with atrial septal defects and aorticopulmonary communication. An inconstant response followed the administration of *l*-norepinephrine in the dogs with ventricular septal defects or mitral regurgitation. Methoxamine hydrochloride, however, resulted in an exaggeration of the shunt and regurgitant flow in each case.

These animal studies suggest that the diagnostic characteristics of indicator-dilution curves with equivocal results or those with lesser degrees of shunt or regurgitant flow may be better defined by temporarily altering the abnormal flow.

Studies on Diet, Physical Activity, and Serum-Cholesterol Concentration

Henry L. Taylor, Joseph T. Anderson, and Ancel Keys, Minneapolis, Minnesota

Five experiments were carried out, each with 5 to 9 normal young men as subjects. A sedentary control period of 2 weeks was followed by a week of conditioning on the treadmill and 2 weeks in which the subjects expended 1,200 calories a day walking 2 hours at 3.5 miles per hour on a 10 per cent grade. The final period of sedentary activity was 2 weeks. The diet during the control period of each experiment contained 40 per cent of calories as fat, principally saturated. During the exercise period, 1,000 calories of the desired composition were added. When fat was used, the composition was that of the fat employed in the control period. Total calories were adjusted to maintain body weight content to $\pm$ 2 pounds. The per cent of calories from fat during the exercise period in 5 experiments was 43, 53, 32, 20, and 55 which produced the following changes in serum-cholesterol concentration at the end of the exercise period: 1.7 mg. per cent, −18.4, −22.5, +3.0, and 1.5. In the last experiment, the recovery diet was maintained at 54 per cent of calories from fat and the serum-cholesterol concentration increased 15 mg. per cent in 2 weeks. It is concluded that when the fat is principally of the saturated variety, the serum cholesterol during moderate work is controlled by the per cent of fat in the diet up to approximately 40 per cent of total calories. After this point, a moderate physical work load results in a lower cholesterol than expected.

Use of Massive Doses of Penicillin in Treatment of Subacute Bacterial Endocarditis in Patients Allergic to Penicillin: Report of Two Cases with Comments on Possible Immunologic Mechanisms Involved

Thomas J. Theobald, New York, New York

Two cases of subacute bacterial endocarditis (SBE) in patients with demonstrated hypersensitivity to penicillin are presented. In the first case, the SBE was superimposed upon a rheumatic valvulopathy; in the second case, upon a patent ductus arteriosus. Penicillin was deemed necessary for therapy in both cases. They were given intravenous aqueous penicillin in doses up to 120 million units per day for 40 days.

Allergic reactions were successfully controlled by prednisone in both cases; an antihistaminic agent was added to the regimen in 1 case. Both patients made a complete recovery.

A minimal effective dose of prednisone was noted to be above 40 mg. per day in divided doses during the early weeks of therapy. It was found that after several weeks on this regimen the need for the steroid ceased. Although the total circulating eosinophil counts rose markedly, no further allergic manifestations were seen, in spite of the continuation of penicillin. Furthermore, when the penicillin was stopped no further allergic signs appeared. Two immunologic mechanisms are suggested to explain the absence of allergic signs in the presence of massive doses of antigen long after any protective influence of steroid was present.

Evidence that Activated Hageman Factor is Associated with a Hypercoagulable State

Duncan Thomas, Stanford Wessler, and Stanley M. Reimer, Boston, Massachusetts

Early in blood coagulation, there is elaborated from inactive precursors a thrombogenic activity (serum thrombotic accelerator, or STA) requiring for its formation prior activation of the initial procoagulant, Hageman factor (HF). Our data suggest that activated HF in vivo reflects a hypercoagulable state with a potential for thrombosis greater than normal.

The normal ratio of glass-to-silicone clotting times in the rabbit is approximately 1:1.75. In studies of the effect of human plasma and serum on thrombogenesis in 116 rabbits, activated HF was associated with abolition of this normal glass-silicone differential. Infusions into rabbits of human, silicone-processed ("intact") plasma or serum, devoid of activated HF and STA, neither abolished the normal glass-silicone differential nor induced thrombosis in areas of retarded blood flow. Infusions of glass-processed ("contact") plasma or serum both removed the glass-silicone differential and initiated thrombosis. In contrast, infusions of plasma or serum preparations containing activated HF but no STA eliminated the glass-silicone differential, but were not thrombogenic. Finally, congenital STA-deficient plasma infusates, in contrast with HF-deficient plasma, abolished the glass-silicone differential, although neither induced thrombosis.

Loss of the normal glass-silicone differential has been observed in the blood of patients with thromboembolism. In 9 rabbits with enteric infections, control glass and silicone clotting times were identical, and single infusions of "intact" serum initiated thrombosis. Moreover, in healthy rabbits, infusions of activated-HF plasma preparations (free of STA) followed by "intact" serum infusions produced thrombosis, whereas neither infusate alone was thrombogenic. It is concluded that this may be the first demonstration of a possible role of Hageman factor in thrombogenesis.

Evidence of Extrarenal Action of Mercurial Diuretics

Sam A. Threefoot, New Orleans, Louisiana

Observations of increased flow of fluid from needle tracts of paracenteses and from Southey's tubes following parenteral administration of mercurial diuretics prompted investigation of the "local" action of these drugs. One-tenth ml. 4 per cent T 1824 injected at 2 adjacent sites, intradermally, produced a stained area; 24 hours later, a dry needle puncture and intradermal injections of 0.02 ml. saline, epinephrine, histamine, hyaluronidase, theophylline ethylenediamine, mercaptomerin, and meralluride were performed around its periphery. Results were similar for all 5 subjects studied. Some slight and/or temporary clearing of dye occurred at all injection sites, but was increasingly distinct and permanent with mercaptomerin, theophylline ethylenediamine, and meralluride. Additional studies were conducted on urinary excretion of Patent Blue V (PBV) after intradermal injection with and without injection of drugs at the same site. All 4 edematous subjects and 3 of 4 nonedematous subjects demonstrated an increased excretion of dye after accompanying injection of 0.05 ml. meralluride. Similar quantities of theophylline ethylenediamine or mercaptomerin did not produce increased excretion. The degrees of clearing observed with each of these and the fact that meralluride contains theophylline suggested that theophylline was responsible for, or at least potentiated, the clearing action of the mercurial diuretic. The studies on excretion of PBV did not substantiate this, however, but gave further supporting evidence that meralluride, injected in a quantity too small to be exerting a renal effect, produced increased uptake of dye from the local site.

Secondary Malignant Tumors of the Pericardium: A Clinicopathologic Study

Deloran L. Thurber, Jesse E. Edwards, Howard B. Burchell, and Richard W. P. Achor, Rochester, Minnesota

Although pericardial metastasis is a not uncommon observation at necropsy on patients with malignant neoplasia, antemortem recognition is infrequent. Establishing this diagnosis has become more important because recent improvements in treating malignant disease may afford valuable palliation. Consequently, this study was undertaken to define more clearly the clinical manifestations of pericardial malignant disease.

Among consecutive necropsies performed from 1942 through 1958, 189 cases of secondary pericardial malignancy were found. The primary malignant lesions responsible for two-thirds of the pericardial lesions were: pulmonary carcinoma, 52 cases (28 per cent); lymphoma, 38 cases (20 per cent); and mammary carcinoma, 35 cases (19 per cent).

In 55 (29 per cent) of these 189 patients, impairment of cardiac function was considered to be due to 1 or more of the following mechanisms: pericardial effusion, 30 patients (55 per cent); myocardial invasion, 28 (51 per cent); encroachment on great vessels of the heart, 13 (24 per cent); neoplastic cardiac constriction, 12 (22 per cent); and invasion of coronary veins, 2 (4 per cent).

The most frequently recorded clinical manifestations which might have resulted from the pericardial malignancy were dyspnea, cough, pleural effusion, hepatomegaly, and thoracic pain. Electrocardiograms were available on 27 of the 55 patients. Twenty-five (93 per cent) had T-wave abnormalities; 22 (81 per cent), low QRS voltage; 6 (22 per cent), S-T segment depression in the standard leads, and none had S-T segment elevation. Thoracic roentgenograms on 53 patients demonstrated cardiac enlargement in 15 (28 per cent) and mediastinal abnormalities in 11 (21 per cent).

Blood-Flow Measurements in the Lower Human Extremity Before and After Lumbar Sympathectomy

David A. Tice, Italo Besseghini, George E. Reed, and Walter Redisch, New York, New York

Blood flow to the lower extremity was measured plethysmographically at 20 C. and at 25 C. in 4 patients with documented nongangrenous obliterative arterial disease; the distribution of blood to 2 vascular beds, the skin-subcutis, and the skeletal muscle was estimated. Responses to body warming, regional exercise, and infusion of norepinephrine were measured. Systemic arterial pressure and surface temperature were monitored.

After the initial measurements were completed, the studied limb was subjected to lumbar sympathectomy: the lumbar ganglia from above the first to below the fourth were resected. Ten to 12 days after the operation, the measurements were repeated. The pertinent findings were that total resting perfusion of the limb was invariably higher after than before sympathectomy. The vasodilator reflex response to body warming was regularly inverted after sympathectomy; both skin and muscle beds participated in this postsympathectomy vasoconstrictor response. Vascular responses to exercise were not altered by sympathectomy. The vasoconstrictor response to norepinephrine was even more marked after sympathectomy than before, somewhat more so in the muscle than in the skin. Surface temperature responses to change in environmental temperature were markedly diminished, if not entirely abolished, after sympathectomy. There were no appreciable changes in systemic (brachial) arterial pressure, except for the systolic and diastolic increase recorded regularly during norepinephrine infusions.

Acetylcholine-Induced Atrial Fibrillation In Vivo

Marylouise Torchiana and Evangelos T. Angelakos, Boston, Massachusetts

Acetylcholine was infused in vagotomized, pentobarbital-anesthetized dogs and the electrical threshold to excitation was determined with rectangular 3-msec. pulses delivered through a bipolar electrode attached on the left atrium. Prior to acetylcholine infusion, threshold stimuli delivered in all parts of the cardiac cycle did not produce atrial fibrillation. During constant acetylcholine infusions of 25 to 35 μg./Kg./min., threshold stimuli produced atrial fibrillation only when delivered within the relative refractory period. However, with 50 μg./Kg./min., atrial fibrillation was also produced by threshold stimulation during the diastolic period. This effect was more pronounced when acetylcholine infusion was continued for over 1 hour. Any electrical stimulation during infusion of more than 100 μg./Kg./min. resulted invariably in atrial fibrillation. Atrial fibrillation was terminated by discontinuing both acetylcholine infusion and electrical stimulation.

Acetylcholine infusion greater than 25 μg./Kg./min. produced shortening of the refractory periods, but no change in diastolic threshold. Atropine (0.01 mg./Kg.) blocked both the changes in refractoriness and predisposition to atrial fibrillation.

This study confirms previous findings obtained in vitro and suggests that endogenous acetylcholine may play a role in the development of atrial arrhythmias and fibrillation in vivo.

Classic Mitral Commissurotomy in Patients Aged Fifty Years and Over: 100 Consecutive Cases

Robert G. Trout, Julio C. Davila, Philadelphia, Pennsylvania, and Robert P. Dobbie, Bethesda Maryland

With the general advance in the age of the population, better diagnostic methods, and safer technics in anesthesia, the scope of valvular surgery has been extended into the older patient to a considerable degree. Over 100 patients have

been operated upon to the present time, the oldest aged 64 years, with the average 54 years. The results, early and late, with follow-up data over 5 years in approximately one-half the series is reported. Early and late mortality by stages is discussed as a guide for selection of cases. Combined aortic and mitral commissurotomies in patients over 50 is briefly mentioned as a separate group.

Two-Chambered Right Ventricle: Report on Seven Patients

Argyrios A. Tsifutis, Alexis F. Hartmann, Jr., and Hakan Arvidsson, St. Louis, Missouri

The division of the right ventricle into 2 chambers by hypertrophic muscular bands is a very unusual congenital cardiac malformation which may be mistaken for tetralogy of Fallot or an interventricular septal defect; but cardiac catheterization, and especially selective angiocardiography, will establish the correct diagnosis. The muscular bands divide the right ventricle into a high-pressure chamber immediately distal to the tricuspid valve, and a low-pressure chamber bounded by these bands and the pulmonic valves. This malformation may occur as the only defect, but it is often associated with an interventricular septal defect which may be located at the junction, above or below the plane of the hypertrophied muscular bands.

This is a report about 7 patients (aged 2 to 10 years) with this anomaly in whom the diagnosis was established by cardiac catheterization and selective angiocardiography. All patients had a loud left basilar systolic murmur and thrill, and the second sound in this area was diminished in intensity. The electrocardiogram was within normal limits in 4 patients, 1 showed right ventricular enlargement, 1 was suggestive of this finding, and 1 showed incomplete right bundle-branch block.

Cardiac catheterization revealed pressures in the high-pressure chamber of 55/0 to 133/0 mm. Hg, while the pressures in the distal chamber were 24/0 to 49/0 mm. Hg. Five of the 7 patients had an associated interventricular septal defect and the flow was left to right.

Three of the patients were successfully operated upon with the aid of extracorporeal support. The ventricular septal defect was repaired when the hypertrophied muscular bands were resected.

Periodic Circulatory Changes of Cheyne-Stokes Respiration

Donald H. Tucker, Charles R. Merwarth, and Herbert O. Sieker, Durham, North Carolina

Although phasic changes of pulse rate, blood pressure, and regional blood flow have been reported with Cheyne-Stokes respiration, there have been few observations of overall circulatory effects. In order to evaluate cyclic changes of the circulation in Cheyne-Stokes respiration, the cardiac output (dye method), blood pressure, pulse rate, peripheral blood flow, and arterial blood gases were determined during the periods of hyperpnea and apnea. Observations were made on 8 patients with Cheyne-Stokes respiration due to a cardiovascular or cerebrovascular disease, and on 3 normal subjects who mimicked this type of periodic breathing.

Most patients showed hypocapnia and moderate hypoxemia, and the arterial carbon-dioxide tension was highest and oxygen saturation lowest during the hyperpneic phase. The arterial pressure rose (mean Δ 11 mm. Hg) during hyperpnea, while the pulse rate was unchanged or decreased. The arm blood flow measured by plethysmography increased (mean, 38 per cent) in hyperpnea. The cardiac output was essentially unchanged in congestive-heart-failure patients during the 2 phases of respiration, but it decreased (mean Δ 0.62 L./min.) during hyperpnea in individuals with cerebrovascular disease. Cardiac output increased 1.96 L./min. during hyperpnea in 1 uremic patient. In normal subjects imitating Cheyne-Stokes respiration, the arterial carbon-dioxide tension was lowest during hyperpnea, at which time the blood pressure increased and arm blood flow decreased. The pulse rate and cardiac output, however, were not significantly altered.

These findings indicate that Cheyne-Stokes respiration is associated with phasic alterations in the circulation which appear to be primarily the result of changes in regional blood flow and resistance, and are not determined by consistent variations of the cardiac output.

Effects of $NaHCO_3$, HCl, and Ca Gluconate Infusions on Serum Electrolyte Levels and Blood pH, Strength of Myocardial Contractions, Blood Pressure, Right Atrial Pressure, Electrocardiogram, Catecholamines, and Corticoids

Frank H. Tucker and James D. Hardy, Jackson, Mississippi

The effects of respiratory and metabolic acidosis on cardiac output have been accorded special attention in recent months. The present study was undertaken specifically to delineate the effect of metabolic acidosis (without hypoxia) upon the strength of myocardial contractions. A more general objective was that of monitoring the other parameters listed in the title.

Three groups of 5 normal mongrel dogs were used. Ureters were ligated. Myocardial contractile force (MCF) was measured using the Walton-

Brodie strain-gage arch; right atrial pressure (RAP), blood pressure (BP), and electrocardiogram with the Sanborn recorder; blood pH with the Beckman pH meter; electrolytes, catecholamines, and corticoids as routine for our laboratory. Group I–5 animals infused with $NaHCO_3$ to death; Group II–0.1 N HCl; Group III–Ca gluconate.

A massive number of data were recorded. Alkalosis: MCF well sustained until severely increased pH just before death. BP–wide pulse pressure; RAP–variable; serum: Na increased, Cl decreased, Mg decreased, Ca decreased, K variable. Acidosis: MCF and BP rather well sustained until marked decrease in blood pH (e.g., 6.6); serum Na decreased, Cl increased (slight), CO_2 decreased (marked), Mg variable, Ca decreased, K increased. Hyperealcemia: MCF increased and BP increased initially, pH decreased, Na decreased, Cl decreased, K same.

It is concluded that alkalosis and acidosis do not seriously impair the strength of myocardial contractions until marked pH changes have been produced. Calcium infusion initially increased the strength of MCF by a factor of 2.9. Acidosis markedly increased catecholamine elaboration.

Different Role of Capillary Permeability in Edema of Heart Failure and Renal Disease

John Tuckman and Frank A. Finnerty, Jr., Washington, District of Columbia*

Two-hour arterial dilution curves of simultaneously administered I^{131}-HSA and Cr^{51}-RBC in 8 edematous patients with heart failure and 6 edematous patients with chronic renal disease were compared with curves of 7 normal patients. In the patients with heart failure, the mixing times of both isotopes were slower than those of normal subjects, but the time for completion of rapid mixing was similar for both isotopes in 6 of these 8 patients. In the patients with renal disease, the time required to complete the rapid mixing of Cr^{51}-RBC was not longer than in normal subjects. On the other hand, in 5 of the 6 patients with renal disease, I^{131}-HSA took longer than normal and conspicuously longer than Cr^{51}-RBC to complete the period of rapid mixing.

It would seem from these data that although capillary permeability to protein does not play an important role in the production of edema of heart failure, it may be significant in the pathogenesis of edema due to chronic renal disease.

Hemodynamic Changes Caused by Sodium Amobarbital in Hypertension

John Tuckman and John P. Shillingford, London, England

The introduction of the dye Coomassis Blue and the development of a linear earpiece recording system have made possible a more complete cardiovascular study of many drugs. With their use, it is possible to obtain frequent indicator-dilution curves and from them accurately calculate relative changes in cardiac output without calibration of the curves, arterial puncture, or blood loss.

Twelve hypertensive patients were investigated during slow intravenous administration of 50 to 500 mg. of sodium amobarbital. Most patients experienced only drowsiness, but some reached a level of light hypnosis. During the procedures, at least 6 and as many as 10 cardiac-output determinations were made. The control arterial pressures were:

average, $\frac{213\ (265\text{ to }145)\text{ mm. Hg}}{118\ (150\text{ to }\ 90)\text{ mm. Hg}}$ and were reduced to: average, $\frac{167\ (215\text{ to }130)\text{ mm. Hg}}{108\ (140\text{ to }\ 85)\text{ mm. Hg}}$; the per cent changes were:

average, $\frac{22\text{ per cent }(34\text{ per cent to }14\text{ per cent})}{9\text{ per cent }(19\text{ per cent to }0\text{ per cent})}$.

The decreases in pulse pressures were: average, 35 (50 to 20) mm. Hg and the per cent changes were: average, 39 per cent (58 per cent to 9 per cent). The cardiac output decreased in all patients; average decrease was 16 per cent (–22 per cent to –8 per cent). The right-atrium–right-ear "central volume" decreased in all patients; average decrease was 10 per cent (–16 per cent to –5 per cent). The changes in arterial pressure, cardiac output, and "central volume" were statistically significant ($P < 0.01$). The systemic peripheral resistances were not significantly changed; average change was + 2 per cent (+6 per cent to –6 per cent). The average of the control heart rates was 71/min. (88 to 55/mm.) and was not significantly changed during sodium amobarbital administration: average, 69/min. (84 to 56/mm.). The control atrial pressures were:

average, $\frac{+\ 6.2\ (+10.5\text{ to }+3.2)\text{ mm. Hg}}{+\ 0.1\ (+5.0\text{ to }-2.0)\text{ mm. Hg}}$ and changed to:

average, $\frac{+\ 3.7\ (+7.5\text{ to }-1.0)\text{ mm. Hg}}{-\ 2.2\ (0.0\text{ to }-5.0)\text{ mm. Hg}}$.

The data presented here strongly indicate that under the conditions of these procedures, the decrease in arterial blood pressure caused by sodium amobarbital is due to a decrease in cardiac output unaccompanied by change in systemic resistance.

Hypocholesterolemic Effect of Sodium Dextrothyroxine

Naip Tuna,† Minneapolis, Minnesota

Sodium dextrothyroxine, 4 to 6 mg. daily, was used in 25 patients with hypercholesterolemia,

coronary atherosclerosis, and angina pectoris, for periods ranging from 2 to 13 months (mean: 6½ months). Three patients had hypothyroidism and were on thyroid extract, while 2 patients had mild diabetes mellitus requiring no insulin therapy. Nine patients were females and 16 were males. The average age of the patients was 57 years (range: 37 to 78). In each case, the serum cholesterol was determined once a week, 4 to 6 times before and 4 times after sodium dextrothyroxine therapy. Later, determinations were done once a month. After therapy, in 20 patients, the serum cholesterol showed a mean decrease of 22 per cent (range: 12 to 48 per cent), while in 5 patients there was no effect even after the dose of sodium dextrothyroxine was increased to 8 mg. daily. Decrease in serum cholesterol was generally first noted 2 weeks after the beginning of sodium dextrothyroxine administration.

Sodium dextrothyroxine was discontinued in 3 patients because of increase of angina pectoris after therapy. In 1 case, after an initial increase following therapy, angina pectoris decreased in spite of continuation of sodium dextrothyroxine. In 2 patients, the serum cholesterol increased to control levels after first showing significant decreases lasting from 2 to 5 months. One patient died of myocardial infarction while on sodium dextrothyroxine.

Role of the Pulmonary Lymphatics in Chronic Pulmonary Edema

Herman N. Uhley, Sanford E. Leeds, Meyer Friedman, and John J. Sampson, San Francisco, California

Studies have shown that canine pulmonary lymph flow increased with *acute* elevation of left-atrial pressure; however, the absolute lymph flow was small and ineffective in preventing acute pulmonary edema. The purpose of the current study was to determine the role of pulmonary lymphatics in *chronic* pulmonary edema in the dog. Chronic pulmonary edema was induced by creating an aorticocaval anastomosis and administering desoxycorticosterone trimethylacetate and a salt-rich diet. Pulmonary lymph flow was measured by cannulating a lymph-collecting chamber produced in the right external jugular vein. Chemical and enzyme determinations of the blood and lymph and histologic studies of the lungs were made. The dogs showed gradual edema, ascites, and weight gain within a period of 1½ to 11 months. Pulmonary edema was found in 10 dogs as evidenced by either lung/body weight ratios or water content of lung biopsies greater than normal. Elevated left-atrial pressures were recorded in several of the animals. Seven of the dogs had striking increases in pulmonary lymph flow ranging from 300 to 2,800 per cent over the normal flow of 4 ml./hr. The study demonstrates the expansion of the pulmonary-lymphatic drainage system and implies that such expansion occurs as a compensatory mechanism for prevention of overt or fatal pulmonary edema when there is an increase of pulmonary venous pressure.

Effect of a Pressure Suit on Cardiodynamic Changes Occurring During Passive Tilt in Healthy Subjects and in Patients with Traumatic Quadriplegia

Carlos Vallbona, David Cardus, William A. Spencer, John Dale, and Morris Burns, Houston, Texas

The heart rate, systolic and diastolic blood pressures, and the time of systole were measured in the supine position and at 60-degrees tilt (feet down) in 20 young men and in 12 male patients with traumatic quadriplegia. These measurements were repeated in the same positions after the subject had been fitted with an inflated pressure suit.

The effects of passive tilt without the pressure suit were: In the healthy subjects the heart rate increased from 60 to 80 beats per minute; systole shortened by 0.039 second; the blood pressure remained unchanged. In the quadriplegics, the rate increased from 66 to 92; systole shortened by 0.048 second; and the blood pressure decreased from 118/74 to 81/49.

Effects of inflation of the pressure suit were: Inflation at zero degrees did not change the cardiodynamics in the healthy subjects; in the quadriplegics, there was a slight increase in systolic and diastolic pressures.

Effects of passive tilt with the pressure suit inflated were: In the healthy subjects, the heart rate increased from 59 to 69 beats only; the rate increased from 61 to 82 in the quadriplegics, and the blood pressure decreased from 132/87 to 105/71 only. Although the heart-rate increase and blood-pressure decrease in the quadriplegics were less than during passive tilt without a pressure suit, there was a significant shortening of the time of systole ($P < 0.001$).

Sudden deflation of the suit while the subject was at 60-degrees tilt produced heart-rate increase, systole shortening, and blood-pressure decrease. These effects were greater in the quadriplegics. These results indicate that an inflated pressure suit permits the quadriplegic patient to maintain cardiodynamic values, during passive tilt, that approximate those of the healthy subjects.

Studies on Variability of Heart Rate at Birth in Healthy Infants and in Infants with Respiratory Distress

Carlos Vallbona, Murdina M. Desmond, Robert R. Franklin, Reba M. Hill, and John Rush, Houston, Texas

Cardiotachometric tracings were obtained at random intervals from 30 minutes before birth to 6 hours after delivery in 27 full-term infants born by vaginal delivery. Twenty of these infants fulfilled "standard" criteria of health. Seven infants presented different degrees of respiratory distress.

Observations in the "healthy" infants: Prior to delivery, episodes of gradual deceleration of the heart rate were recorded during uterine contractions. Immediately after delivery, sudden, brief episodes of deceleration were noted in some infants coincidental with clamping of the umbilical cord and suction of the upper airway. A rapid phase of acceleration was noted to follow these initial episodes. The acceleration occurred very rapidly and resulted in an average peak value of 174 beats per minute at the age of 2 minutes. During this phase, respiratory fluctuations in the duration of the cardiac cycle were not elicited. The phase of deceleration started at the age of 8 minutes. Numerous sudden, brief episodes of acceleration or deceleration were noted superimposed on the overall trend of deceleration. These episodes did not correlate with specific types of motion and in many instances they were observed when the infant was quiet.

Observations in the infants with respiratory distress: The fetal cardiotachograms showed essentially the same fluctuations observed in the healthy infants. The episodes of deceleration produced by suction of the airway or clamping of the cord were more intense and of longer duration. The phase of acceleration occurred less rapidly and it yielded a peak value of heart rate of 156 per minute at the age of 4 minutes. The phase of deceleration was characterized by the paucity of fluctuations in heart rate. When present, they were usually of deceleration, but they were smaller and lasted longer than those recorded in healthy infants.

These observations suggest that infants with respiratory distress have a lesser activity of the centers regulating the activity of the cardiac pacemaker.

Pathogenesis of Simple, Complete, and Corrected Transposition of the Great Vessels (P)

Lodewyck H. S. Van Mierop, Montreal, Canada, Ralph D. Alley, Harvey W. Kausel, and Allan Stranahan, Albany, New York

Although transposition complexes are among the most important, common, and puzzling congenital cardiac anomalies, there is no generally accepted explanation of their pathogenesis. One may conclude that important gaps or errors must exist in modern concepts of cardiac embryology.

In an effort to gain a more detailed knowledge of cardiac development, 21 serially sectioned embryos ranging in size from 6.7 to 40 mm. C-R (crown-rump) length have been studied and wax reconstructions made of representative specimens.

On the basis of these investigations, it was found that the only true transposition complexes are the complete and corrected types. The former is due to maldevelopment of the terminal truncus area, the latter to a reversed loop formation of the primitive heart tube. Dextroposition of the aorta, simple transposition, and Taussig-Bing complex appear to have an entirely different pathogenesis.

Pathologic Anatomy of Single Ventricle (P)

Richard Van Praagh, Patrick A. Ongley, and Harold J. C. Swan, Rochester, Minnesota

In single or common ventricle, the atrioventricular valves, either separate or common, open into a large ventricle which usually is associated with a diminutive outlet chamber. The great arteries, which are frequently transposed, may arise from the large, the small, or both chambers. These hearts have been classified in terms of their ventricular anatomy and great-artery interrelationships. The gross morphology of right and left ventricle is distinctive. Right ventricular trabeculae are relatively coarse, whereas left ventricular trabeculae are relatively fine. The right ventricular aspect of the ventricular septum is entirely trabeculated. The upper half of the left ventricular aspect is smooth. These characteristics were utilized to elucidate the ventricular myocardial composition of 16 hearts with single ventricle (groups A to D): (A) 10 hearts showed a large morphologic left ventricle and a small anatomic right ventricle; (B) 1 heart exhibited a large morphologic right ventricle and a small anatomic left ventricle; (C) 3 hearts displayed approximately equal amounts of right and left ventricular myocardium; (D) in 2 hearts, the ventricular myocardium was undifferentiated and no ventricular septum was identified. In the remaining 14 hearts, the ventricular septum was defective and was displaced and angulated relative to the normal atrial septal plane.

The great-artery interrelationships were: in group A—normal, 4; transposition, 2; inverse transposition, 4; in group B—normal, 1; in group C—transposition, 1; inverse transposition, 2; in group D—transposition, 2.

These findings may be explained by incomplete dextrorotation or levorotation of the primitive ventricular loop and bulbus cordis, and may be expressed in simple geometric terms.

Concealed Ventricular Automaticity During Ouabain Administration

Mario Vassalle and Kalman Greenspan, Brooklyn, New York

Transmembrane-potential records of isolated preparations of canine heart demonstrate a toxic effect of ouabain on Purkinje fibers, characterized by enhanced pacemaker activity, at a time when ventricular action potential reveals no toxic changes. Studies of intact, anesthetized dogs also show that ouabain administration causes enhanced automaticity in Purkinje fibers before the electrocardiogram reveals any disturbance of rhythm. This enhanced, but concealed, ventricular automaticity is revealed by vagal stimulation which causes either sinus arrest or atrioventricular block. Early during ouabain administration, the time interval from onset of vagal stimulation to ventricular escape diminishes progressively, the idioventricular rate increases progressively, and the number of active pacemaker sites in the ventricle increases. Only after additional administration of ouabain does the ventricular automaticity become evident in the absence of vagal stimulation; at this stage, single or multiple ventricular complexes interrupt the normal sinus rhythm. In some instances, these ventricular complexes disappear with vagal stimulation and may represent re-entry beats. During severe intoxication, the automaticity of individual ventricular foci shows a periodicity similar to that recorded from isolated preparations. At the height of ouabain toxicity, KCl infusion caused a decrease in ventricular automaticity revealed by a return to sinus rhythm and subsequently, during vagal stimulation, a progressive slowing of idioventricular rhythm. During KCl intoxication, when P waves were absent from the electrocardiogram vagal stimulation still caused cardiac arrest. When KCl caused cardiac arrest, stimulation of the ventricular myocardium elicited electrical and mechanical responses, demonstrating a selective depolarization of specialized pacemaker tissues by potassium.

Problems Associated with the Use of Acid Citrate Dextrose Formula B (ACD) Blood in Open-Heart Surgery

Robert S. Venerose, Jackson H. Stuckey, Martin Seidenstein, and Karl E. Karlson, Brooklyn, New York

Ten adult mongrel dogs underwent total body perfusion for 30 minutes at normothermic temperatures. All blood used in this experiment was collected in Acid Citrate Dextrose Formula B (ACD), as used in the Kings County Hospital Center blood bank, and stored for 1 to 6 days. Four units of blood were used to prime the circuit; 30 mg. of heparin and from 0.2 to 1.0 Gm. of $CaCl_2$ were added to each unit of blood used in the circuit. Lead II of the standard electrocardiogram and femoral-artery pressure were monitored throughout. Serum K, Na, CO_2, Cl, Ca, along with the pH, plasma hemoglobin, and hemoglobin were determined on the priming blood, the perfusion dog at various intervals before, during, and after perfusion, and on the donor dogs. At the end of the perfusion, the excess heparin was neutralized with protamine. A comprehensive blood coagulation work-up preperfusion and 2 hours' postperfusion were carried out in each dog.

Of the 10 dogs perfused, 9 survived for 24 hours or longer and were sacrificed at specific intervals. Two dogs showed evidence of metabolic acidosis after conclusion of the perfusion; the single operative mortality was in this group. The changes in blood-coagulation data obtained postoperatively in all the animals are similar to those seen when freshly drawn heparinized blood is used. From these results, it may be stated that it is possible to perfuse dogs with ACD blood and have them survive. The problems encountered in this study are undergoing further evaluation.

Diagnosis of Thrombosis of the Left Atrium in Rheumatic Heart Disease

Albert G. Vitale, New York, New York

One of the known complications of rheumatic mitral valvular disease is thrombosis of the left atrium. Ordinarily, this feature of the disease is recognized at postmortem examination or upon entry into the atrium during mitral valvuloplasty. In the latter instance, satisfactory valvuloplasty is technically more difficult, or impossible.

A diagnostic constellation for left-atrial thrombosis has been evolved from detailed evaluation of the history, clinical, physiologic, and radiologic findings in a series of patients studied as candidates for mitral-valve surgery. Criteria for diagnosis consisted of the following: (1) suggestive common features in the natural history of the heart disease in these patients; (2) a striking consistent deformation of the barium-filled esophagus coupled with frequent demonstration of left-atrial or mitral-valve calcification on routine fluoroscopy and conventional x-ray films; (3) characteristic qualitative pattern of the pulmonary wedge catheter tracing; and (4) demonstration of filling defect in the left atrium via selective angiocardiography.

The data on 7 patients is presented in whom left-atrial thrombosis was predicted and subsequently verified either at operation (5 patients) or upon postmortem examination (2 patients). The importance of the diagnosis of the left-atrial thrombosis, with particular reference to its surgical implications, is discussed.

Congenital Aortic Stenosis Studied by Retrograde Arterial Catheterization: Correlation of Electrocardiographic Findings, Symptoms, and Severity of Obstruction (P)

Peter Vlad, Franco Legnami, Norman B. Thomson, and Edward C. Lambert, Buffalo, New York

In an attempt to determine the relationship between the clinical and laboratory findings and the degree of stenosis, 56 infants and children with congenital aortic stenosis were studied by retrograde arterial cardiac catheterization. In only 4 of 52 cases approached from the right arm could the left ventricle not be entered. Conversely, all 4 tests performed through the femoral or left brachial artery failed. In all 48 successful cases, the sites of obstruction could be localized by pressure studies and selective angiocardiography.

Peak pressure gradients between the left ventricle and the central aorta were correlated with the electrocardiographic findings. There were 31 instances in which the electrocardiographic tracings were interpreted as normal. In 14 of these patients (45 per cent), the gradients were over 51 mm. Hg; 3 of this group had gradients of over 80 mm. Hg. On the other hand, our data show that when the electrocardiogram showed evidence of left-ventricular hypertrophy, moderate or severe stenosis was present in all but 3 of 25 cases.

There was less correlation of symptoms with the degree of obstruction as measured by pressure gradients, in that 18 of 36 patients (50 per cent) with moderate or severe stenosis were entirely asymptomatic. Of additional interest is the fact that 7 patients (13 per cent) were both asymptomatic and had normal electrocardiograms, despite pressure gradients of 70 mm. Hg or more.

The above data strongly indicate that children with severe congenital aortic stenosis are frequently asymptomatic; furthermore, unlike the situation which exists with regard to pulmonic stenosis, the electrocardiogram commonly *fails* to reflect the severity of the stenosis. This is contrary to most current thinking. In view of these findings, we believe at present that *all children* with a murmur of aortic stenosis should be studied by left-heart catheterization to determine the need for surgery.

Importance of Left-Heart Catheterization in Congenital Aortic Stenosis

John H. K. Vogel, John T. Leahy, and S. Gilbert Blount, Jr., Denver, Colorado

Vagaries in the clinical evaluation of patients with congenital aortic stenosis, the possibility of sudden death in these patients, and recent advances in the surgical correction of this defect have led us to direct measurement of the pressure gradient across the aortic valve. In 16 patients studied, left-ventricular pressures were obtained by transseptal puncture (7), percutaneous left-ventricular puncture (7), and retrograde catheterization of the left ventricle via a systemic artery (2). Cardiac outputs by direct Fick or indicator-dilution techniques were obtained and, in some instances, the aortic pressure gradient was further evaluated during an isoproterenol-induced high-output state.

In 9 patients with normal electrocardiograms, 4 had severe gradients (75 to 116 mm. Hg) across the aortic valve, and 5 had mild gradients (22 to 30 mm. Hg). Of 5 patients with electrocardiograms suggesting left-ventricular hypertrophy by voltage only, 2 had mild gradients (23 to 34 mm. Hg), 2 had moderate gradients (53 to 60 mm. Hg), and 1 was severe (75 mm. Hg). Two patients with definite left-ventricular hypertrophy by electrocardiogram had previously had ligation of a large patent ductus arteriosus and their aortic pressure gradients were 26 and 50 mm. Hg.

Therefore, the electrocardiograms in these patients did not provide reliable evidence of the severity of congenital aortic stenosis. Further, careful evaluation of the history, physical findings, x-rays, and phonocardiograms did not distinguish the patients with small from those with large gradients, except the systolic murmur tended to be longer in severe stenosis.

Thus, severe congenital aortic stenosis may exist, and yet its magnitude may not be reflected even by careful clinical examination. Direct measurement of the pressure gradient across the aortic valve is of great value in assessing these patients.

Anaerobic Cardiac Metabolism During Severe Hypoxia (P)

Heinz Vollenweider and Walter F. Ballinger, II, Philadelphia, Pennsylvania

The myocardium continues to perform work during brief periods of hypoxia. Calculation of arteriovenous differences of excess lactate in the coronary circulation permits an estimate of the role of anaerobic metabolism in the maintenance of cardiac function.

Experiments were carried out upon 8 mongrel dogs under pentobarbital anesthesia with succinylcholine. Mechanical ventilation was used. Samples of arterial blood were obtained at 1- to 2-minute intervals during normal ventilation and during periods of hypoxia induced by cessation of ventilation. Samples were obtained simultaneously from the coronary sinus. Oxygen, carbon dioxide, lactate, and pyruvate contents of the blood were determined. Excess lactate was calculated using the formula of Huckabee.

The respiratory quotient of the myocardium remained lower than 1 until the oxygen content of arterial blood fell below 5 volumes per cent. Above this level, the myocardium functioned aerobically, as shown by the lower level of excess lactate in coronary sinus blood than in arterial blood. After more than 2 minutes of ventilatory arrest, the arterial oxygen content fell below 5 volumes per cent and the respiratory quotient rose above 1 in

all animals. The myocardium produced excess lactate at this stage, indicating that part of the energy was gained from anaerobic metabolism. When ventilatory arrest was prolonged to at least 4 minutes, arterial oxygen content fell below 1 volume per cent. Myocardial metabolism became almost completely anaerobic, yet the heart continued to beat with a normal rhythm for over 2 minutes more before fibrillation occurred. It is suggested that this ability of the heart to function anaerobically permits survival during temporary periods of inflow occlusion, respiratory arrest, and other hypoxic conditions.

Differences in Hypertensive Effect of Norepinephrine Given Intra-arterially and Intravenously

John M. Wallace, Durham, North Carolina, and John H. Sadler, Atlanta, Georgia

Circulating norepinephrine (NE) is rapidly destroyed by the tissues. This effect was studied in the dog by comparing the systemic pressor response produced by injections and infusions of NE into peripheral and central veins with that produced by administration of similar amounts into the left ventricle, the ascending aorta, the abdominal aorta above and below the renal arteries, the brachial and femoral arteries, and the portal vein. One hundred and fifty-nine injections and 182 infusions were given to 40 dogs.

Intravenous and left-ventricular injections produced comparable hypertension, as did infusions into systemic veins and the ascending aorta. Therefore, NE could not have been appreciably destroyed by the blood, by the lungs, or within the chambers of the heart.

Administration into all other arteries gave significantly diminished pressor responses. In some cases no effect was seen. Large infusions were necessary to cause any effect when given into the portal vein.

In 8 dogs, plasma concentrations of NE were measured. Arterial levels were highest during intravenous infusions, much lower during intra-arterial infusions, and lowest during portal-vein infusions.

The tissues effectively remove NE from arterial blood. The portion of arterial NE which reaches venous blood to recirculate is insufficient to maintain a full hypertensive effect. Therefore, an intra-arterial infusion must include a very large portion of the arterial tree in the distribution of the primary infusion in order to produce a full pressor effect. This is emphasized by the observation that infusions into the abdominal aorta, above or below the kidneys, caused less hypertension than infusions into the ascending aorta.

Cardiac Response to Exercise in Unconditioned Young Men and in Athletes

Yang Wang, Minneapolis, Minnesota, John T. Shepherd, Robert J. Marshall, Rochester, Minnesota, Loring Rowell, and Henry L. Taylor, Minneapolis, Minnesota

Cardiac output, stroke volume, and heart rate were studied in 10 males, aged 18 to 24 years, during upright graded exercise on a treadmill. Five were sedentary and 5 were varsity swimmers. Cardiac output was determined by the indicator-dilution method. Top work load was determined by the individual's maximal oxygen intake. At supine rest, the cardiac index (CI) of the sedentary men ranged from 2.6 to 4.2 L./min./M.^{2}, the heart rate (HR) 52 to 75 beats/min., and the stroke index (SI) 30 to 57 cc./M.^{2}. The CI of the athletes ranged from 2.9 to 4.7 L./min./M.^{2}, the HR 51 to 65 beats/min., and the SI 54 to 72 cc./M.^{2}. Standing at rest, the SI fell to from 21 to 44 cc./M.^{2} in the unconditioned men, and to from 34 to 48 for the athletes. At submaximal exercise, during the third minute, the CI of the unconditioned men ranged from 8.3 to 11.8 L./min./M.^{2}, the HR from 186 to 192, and the SI from 43 to 65 cc./M.^{2}. For the athletes, the CI ranged from 9.5 to 14.2 L./min./M.^{2}, the HR from 180 to 197, and the SI from 52 to 79. The values for stroke index during hard exercise averaged not more than 10 per cent above resting supine values in both groups. Athletes do have the advantage of a higher initial SI and lower resting HR, since up to submaximal exercise, CI is probably principally increased through tachycardia. At maximal work, however, there is evidence for a further significant increase in stroke index.

Starling's Law of the Heart in Closed-Chest, Unanesthetized Dogs

J. Richard Warbasse, Eugene Braunwald, and Maurice M. Aygen, Bethesda, Maryland

It is generally agreed that Starling's law applies to heart-lung preparations and open-chest anesthetized dogs. However, there is considerable disagreement about the relevance of the Frank-Starling mechanism to the intact organism. A Kolin-Kado gated sine wave electromagnetic flowmeter was placed around the ascending aortas of 8 dogs. Changes in left ventricular dimensions were recorded with mercury resistance gages. Left ventricular diastolic and intrapleural pressures were measured simultaneously. The chest was closed and the dogs permitted to recover from the anesthesia. Alterations in left ventricular size and effective filling pressure were induced by rapid transfusion or bleeding. Left ventricular stroke

work, mean and peak values of aortic blood velocity and acceleration, and left ventricular power all increased as left ventricular size and filling pressures were augmented. At any given filling pressure and ventricular size, all of these indices of ventricular performance increased during infusion of norepinephrine. These experiments support the view that Starling's law and the ventricular function curve concept are applicable to the heart of the closed-chest, unanesthetized dog with an intact autonomic nervous system.

Normal RS-T Segment Variant

Richard H. Wasserburger, Madison, Wisconsin, and William P. Alt, Muskegon, Michigan

Electrocardiographic data on 48 adults exhibiting elevation of the S-T segment greater than 1 mm. in 2 or more of the precordial leads, V_3 through V_6, are presented. This pattern has been referred to as the "normal RS-T variant." The salient features of this provocative electrocardiographic pattern are:

1. It occurs in approximately 1 per cent of an adult population, and although most commonly seen in the young adult Negro, is present in all age and ethnic groups. The elevated S-T segment usually persists over months to years, with only slight variability.

2. Most typically, the elevated S-T segment is found in precordial leads V_3, V_4, and V_5.

3. Contrary to previous reports, the elevated S-T segment did not consistently return to the isoelectric line following exercise.

4. This pattern is extremely susceptible to T-wave inversion in all leads presenting the elevated S-T variant by means of 10 to 15 seconds of brief hyperventilation. Seventeen of 27 patients so studied showed frank T-wave inversion with this maneuver.

5. Entirely similar T-wave inversion was noted in 8 individuals following both brief hyperventilation and exercise. A reassessment of the various exercise-tolerance tests in the presence of the normal RS-T segment variant is in order.

This electrocardiographic pattern has far-reaching clinical implications, for on occasion it may simulate the injury phase of an active pericarditis or myocardial episode, and if seen in conjunction with the "juvenile pattern" may completely mimic the injury-ischemic phase of an acute myocardial infarction.

Effect of Oral Potassium Salts on Functional and Organic T Waves

Richard H. Wasserburger and John K. Curtis, Madison, Wisconsin

The need for an expedient procedure to clearly differentiate functional from organic T waves in the field of clinical electrocardiography has long been recognized. Based upon our previous experiences with the consistent ameliorating effect of oral potassium salts on functional precordial T-wave inversion, as seen in the "juvenile pattern," 10 Gm. of oral potassium salts have been administered to 100 patients, with clinical and electrocardiographic evidence of the following patterns:

Acute transitory transmural ischemia	18
Acute subendocardial ischemia	10
Acute posterior-wall infarction	15
Acute anterior-wall infarction	15
Healed posterior-wall infarction	5
Healed anterior-wall infarction	5
Left bundle-branch block	10
Left-ventricular preponderance	10
Digitalis effect	10
Pericarditis, subacute	2

Only 4 patients with left-ventricular preponderance and 2 patients with acute, but transitory, transmural ischemia showed improvement, but not normalization of the T-wave inversion. Specifically, the improvement tended to involve only the "fringe areas" of the inverted T waves. All other instances of organic T-wave inversion, irrespective of the etiology, showed no change in polarity or configurations.

Thus, it appears that the oral administration of potassium salts in large dosage is of considerable clinical value in differentiating electrocardiographic T-wave changes of functional origin (anxiety induced) from those with an organic basis. The procedure has been well tolerated and without untoward reaction.

Epicardial Electrocardiographic Potentials in Congenital Heart Disease (P)

Richard H. Wasserburger, William P. Young, Betty J. Bamforth, Lynn K. Hawkins, Karl L. Siebecker, Jr., Madison, Wisconsin, and Jay T. King, Kansas City, Missouri

In an attempt to further define the origin and significance of the various right-precordial QRS complexes presenting in established right-ventricular preponderance (pure R wave, slurred R wave, Rs, rsR′, rR′, and qR patterns), direct right- and left-ventricular epicardial electrocardiographic potentials were recorded on 125 patients with congenital heart disease at time of corrective open-heart surgery. Included in the data were 45 cases of ventricular septal defect, 30 atrial septal defects, and 30 tetralogies of Fallot and/or valvular pulmonic stenotic lesions, respectively.

Measurements of the activation times of all r, R, and r′ or R′ deflections were determined on the

right-ventricular outflow tract potentials. Correlation of the epicardial ventricular potential with the conventional electrocardiogram and the calculated hemodynamic data obtained at time of cardiac catheterization was made.

These data established the rR′ configuration as the presenting QRS complex in right-ventricular preponderance. This complex arises from the high medial outflow tract of the hypertrophied right ventricle (crista supraventricularis muscle bundle). It may present as a pure R, a slurred R, an rR′, or a qR complex in the conventional right-precordial leads. This rR′ complex of right-ventricular preponderance is readily differentiated from incomplete or complete right bundle-branch-block patterns, as characteristically seen with atrial septal defects, by a critical difference in the onset of the activation time of the R′ wave. These data require a complete reappraisal of the many existing criteria for right-ventricular preponderance.

New Method for Continuous Measurement of Adequacy of Cardiovascular Response to Exercise

Karlman Wasserman, Arnold Naimark, and Malcolm B. McIlroy, San Francisco, California

Tests of cardiovascular function based on measurements of heart rate during exercise are unreliable in patients with arrhythmias and other forms of cardiovascular disease. An ideal physiologic test should indicate the work load at which the circulation fails to supply the amount of oxygenated blood demanded by the exercising muscles. When the demand exceeds the supply, anaerobic metabolism develops, lactic acid is formed, and a metabolic acidosis ensues. As a result of CO_2 from bicarbonate buffering of acid adding to CO_2 formed in aerobic metabolism, the amount of CO_2 exhaled per breath increases and the respiratory gas exchange ratio (R) increases above 1.0.

We have used rapidly responding N_2 and CO_2 gas analyzers to measure R, breath by breath, in 6 normal subjects and 19 patients with heart and lung disease, at increasing work loads (bicycle ergometer). In 14 patients and all normal subjects, R increased above 1.0 at submaximal work loads. The work load at which R increased above 1.0 was found to be constant in the same subject. Increased R was due neither to hyperventilation ($P_{A\,CO_2}$ remained normal) nor to arterial anoxemia ($P_{A\,O_2}$ remained normal) and is, therefore, attributed to the development of metabolic acidosis. Arterial blood analyses (11 individuals) confirmed its existence (decreased pH and "standard bicarbonate" coincident with the increase in R).

The unique advantage of this method is that R can be measured continuously by simple gas methods, and metabolic acidosis can be detected as soon as it occurs and related to a specific work load.

Pathogenesis of Human Coronary Artery Atherosclerosis: Demonstration of Serum Lipoproteins in the Lesions and of Localized Intimal Enzyme Defects by Histochemistry (P)

Harvey F. Watts, Philadelphia, Pennsylvania

Naturally occurring human coronary artery atherosclerosis has been studied by histochemical technics and electron microscopy. Using specific fluorescent antibodies against human serum β-lipoprotein (βLP), albumin, and gamma globulin, these substances have been localized in healthy and diseased arteries. The findings indicate:

A normal physiologic perfusion of the vessel wall by plasma proteins from the lumen to adventitial lymphatics occurs in healthy arteries. Transmural passage is directly through the endothelial cells and then within the ground substance which surrounds the intimal cells and fibers and extends through the internal elastic lamina into the muscularis. From there the fluid enters the lymphatics.

Earliest lesions show striking intimal accumulations of βLP in both extracellular metachromatic ground substance and within the smooth muscle cells of the intima. Distribution of βLP corresponds very closely to stainable lipids. More advanced lesions show scarring and lipophages, and less reaction for βLP, apparently indicating breakdown of sequestered lipoproteins.

These findings support the view that blood lipoproteins infiltrating the vessel wall are sequestered by intimal metachromatic ground substance and accumulate there and in the smooth muscle cells giving rise to localized lipid accumulations (atheromas).

Intimal cells show Krebs-cycle enzymes, high-energy phosphatases, and enzymes of fatty-acid oxidation. Focal defects in adenosinetriphosphatase and fatty-acid dehydrogenases occur in the intima, and it is in these enzyme holes that lipid accumulates. These "enzyme lesions" apparently predispose to sequestration and/or prevent metabolic removal of lipoproteins and lead to localized lipid accumulations (atheromas).

Metabolic Effect of an Anabolic Steroid (SC-7525) in Experimental Acute Renal Failure

W. R. Webb and V. deGuzman, Jackson, Mississippi

The objective of this study was to determine the effects of SC-7525 on the metabolism and survival time in experimental acute renal failure.

Forty-one healthy dogs had bilateral ureteral ligation. Groups I and II were given dog food and

water *ad libitum*. Group II had also 100 mg. of SC-7525, intramuscularly, immediately after surgery. Groups III and IV received intravenous fluids of 10 per cent dextrose in water, 30 cc./Kg. body weight daily, but nothing by mouth. Group IV had also 100 mg. of SC-7525 intramuscularly. Blood chemistries included Na, K, Cl, nonprotein nitrogen (NPN), blood urea nitrogen (BUN), creatinine and CO_2, and arterial pH determinations daily. Autopsies were performed on all animals.

Group I showed increasing acidosis, very low CO_2, rise of K up to 19 mEq., moderate decline in Na and Cl, 10-fold rise in NPN, BUN, and creatinine. One-half died by the third, and all by the fourth day. Group II showed half as rapid rise of K, similar rises in NPN, BUN, and creatinine, less decline of CO_2. Three-fourths died by the fourth day. Two dogs lived 5 days and 1 lived 6 days. Group III showed a 60 per cent rise of K, NPN 5 times and creatinine 4 times the control values. Seventy per cent died by the fourth, 85 per cent by the fifth, and all by the sixth day. Group IV showed 52 per cent rise of K up to the fifth day, after which it fell to even less than control value at the eighth to tenth days. BUN and creatinine showed similar rises and later decreases. Na, Cl, CO_2, and weight changed slightly. More than half lived past the sixth day, with 1 living to the tenth day. Autopsy showed right-heart dilatation, severe pulmonary edema, and bilateral hydronephrosis in all groups.

The above observations show that the anabolic steroid, SC-7525, can very significantly retard the accumulation of protein catabolic wastes and significantly prolong life in acute renal failure.

Progressive Pulmonary-Vascular Obstruction in Children with Ventricular Septal Defects

William H. Weidman and James W. DuShane, Rochester, Minnesota

The spectrum of ventricular septal defect includes patients who show evidence of progressive pulmonary-vascular obstructive disease. Repeated cardiac catheterization has led some authors to state that such obstruction virtually never occurs during childhood. Cardiac catheterization is a valuable aid in studying the pulmonary vascular bed but, for various reasons, the data may contain inaccuracies. Recent animal studies have led us to suspect that significant pulmonary-vascular obstruction may escape detection by present cardiac-catheterization technics.

Our experience has proved that the electrocardiogram and thoracic roentgenogram are fully as accurate as cardiac-catheterization data in assessing pulmonary blood flow in children with ventricular septal defects. Thus, the natural history of these children can be documented by careful evaluation of serial roentgenologic and electrocardiographic studies.

This report concerns 6 children with ventricular septal defects in whom cardiac catheterization revealed severe pulmonary-vascular obstructive changes resulting in a pulmonary:systemic blood-flow ratio of less than 1. Serial thoracic roentgenograms showed that all these children had presented evidence at some time of increased pulmonary blood flow, with subsequent progressive pulmonary-vascular disease, as demonstrated by changes in the size of the heart and the main pulmonary artery and in the pulmonary-vascular shadows.

This study demonstrates that progressive pulmonary-vascular obstruction does occur during childhood in some patients with ventricular septal defect, changing a physiologic situation favorable to operation to one that is completely unfavorable with present corrective technics. Such patients should have early repair of their defects in an effort to prevent these changes.

Bacteremic Shock Syndrome

Max H. Weil, Herbert Shubin, Barbara A. Jackson, and Marjory Biddle, Los Angeles, California

Shock is observed with increasing frequency as a complication of overwhelming infections and especially during bacteremia caused by Gram-negative enteric bacteria. The seriousness of this problem is revealed by a study at the Los Angeles County General Hospital, between 1956 and 1960, of 719 consecutive patients from whose blood Gram-negative bacteria were recovered. In 692 of the patients, clinical features corroborated the presence of systemic infection. Shock occurred in 169 patients (24 per cent). *Escherichia coli, Klebsiella-Aerobacter* group, and *Proteus* species were the organisms most frequently involved.

That the bacterial infection was of itself the cause of shock was frequently not recognized. Electrocardiographic evidence of myocardial injury and elevation of serum glutamic oxaloacetic transaminase were present in a majority of patients in whom these parameters were measured; the erroneous impression was often gained that shock had resulted from myocardial infarction.

The mortality of patients with bacteremia alone was 20 per cent, but when bacteremia was complicated by shock it was 80 per cent. In addition to antibiotics and vasopressor agents, corticosteroid hormones were employed for treatment, although selection of patients and dosage schedules were not standardized. In 31 patients treated with hydrocortisone in amounts greater than 300 mg. to

a maximum of 2.5 Gm. per 24 hours, mortality was 45 per cent. In 67 patients who received less than 300 mg., mortality was 85 per cent. These findings are in accord with our studies demonstrating markedly increased survival in dogs, rats, and mice when corticosteroids in large doses are administered early for treatment of shock experimentally produced by *E. coli* endotoxin.

Hemodynamic Studies on Effects of Vasopressor Drugs in Treatment of Shock

Max H. Weil, Robert B. Sudrann, and Herbert Shubin, Los Angeles, California

The fall of blood pressure during shock associated with myocardial infarction or infection does not result from generalized vasodilatation. To the contrary, the predominant change is arterial vasoconstriction. For this reason, the rationale of using sympathomimetic drugs which presumably increase vasoconstriction has been challenged.

Studies in 6 patients during shock, using indicator-dilution technics and intra-arterial pressure recordings, demonstrated markedly reduced cardiac output and increased peripheral resistance. Administration of vasopressor agents (norepinephrine, metaraminol) in moderate doses significantly increased cardiac output, but produced only a relatively small rise in peripheral resistance. As the dose of vasopressor amine was raised and the arterial pressure elevated to "normal" levels, the additional increase in cardiac output was small, while augmentation of peripheral resistance was disproportionately large. These measurements suggested that optimal hemodynamic effects are obtained when the arterial pressure is maintained at a level slightly below that presumed to be "normal" for the individual patient.

Vasoconstrictor effects on arteries and arterioles probably do not account for the major beneficial effects of vasopressor agents. Present evidence indicates that the demonstrated increase in cardiac output is provided by effects of the drug on veins and venules, by which venous return is augmented, and also by a direct action on the heart, resulting in improved myocardial contractility. Sympathomimetic amines have beneficial hemodynamic actions, in patients with shock, which are not directly dependent on their arterial vasoconstrictive effects.

Influence of Age and Sex on Ventricular Ejection Dynamics in Man

Arnold M. Weissler, Barbara K. Kolmen, Galveston, Texas, Walter H. Roehll, Cincinnati, Ohio, and Robert G. Peeler, Durham, North Carolina

In the normal individual, left ventricular ejection time (LVET), determined from carotid pulse tracings, is related inversely to heart rate (HR) and directly to stroke volume (SV). In view of previous observations suggesting sexual differences in LVET, the present study of these relationships in normal adult and prepubertal males and females was undertaken.

The relationships between HR and LVET were studied in 140 adults and 48 children (aged 1 to 8 years) equally divided between the sexes. In the range of HR from 48 to 120 in the adults and 60 to 133 in the children, LVET varied inversely with HR, with an identical slope for the males and females in each group (adult, 0.0016 HR, prepubertal, 0.0013 HR). The differences in the regression relationships between the adult and prepubertal groups were significant ($P < 0.01$). A parallel shortening of LVET, averaging 0.02 second per beat throughout the range of heart rate, was observed in the adult males as compared with the adult females ($P < 0.01$). No such sexual difference in the range of LVET was observed in the prepubertal group.

When flow relationships were considered (15 adult males and 11 adult females), the mean rate of left ventricular ejection (SV/LVET) was consistently lower in the adult female. This difference remained unchanged when the flow data were corrected for weight and body surface area. These observations demonstrate the influence of sex and age on ventricular ejection and suggest the presence of a more rapid rate of left ventricular contraction in the adult male ventricle.

Tissue Electrolytes of Rats Given Chlorothiazide

John M. Weller and Arthur S. Haight, Ann Arbor, Michigan

These studies were done to determine the effect of chlorothiazide on tissue water and electrolytes of normotensive and hypertensive rats. Chlorothiazide (50 to 100 mg./Kg. body weight/day) was administered in food for at least 6 weeks to normotensive rats, and in drinking water (100 to 150 mg./Kg. body weight/day) for 2 weeks to renal hypertensive rats. Mean blood pressure decreased following chlorothiazide ingestion in the hypertensive group, but not in the normotensive group.

Changes in electrolytes in normotensive rats were not striking, but there was a tendency toward hypokalemia and hypochloremia in plasma. Alterations in skeletal muscle were similar, but changes in heart muscle and aorta were not consistent. In hypertensive rats, changes in plasma and skeletal muscle were minimal, but the potassium and water contents of aorta decreased.

Factors Determining Variability of Blood Viscosity in the Peripheral Circulation

Roe E. Wells, Jr., Boston, Massachusetts, and Edward W. Merrill, Cambridge, Massachusetts

The viscosity of whole blood is a function of the concentrations of its cellular and plasma elements. Because blood is a complex fluid consisting of a suspension of cells in a protein solution, its viscosity is also dependent upon the conditions of flow under which it operates. Viscosity can be quantitated if the frictional (shearing) forces within the fluid during flow can be measured in relation to the rate at which these forces occur. Rate of shear in the peripheral circulation is a function of vessel radius and flow velocity. Blood viscosity was measured in a viscometer capable of quantitating shear stress at various specified rates of shear. Untreated whole blood is demonstrated to be a shear-thinning fluid, i.e., its viscosity decreases as shear rate increases. Since shear rate is determined by vessel dimension and flow velocity, it was demonstrated that blood viscosity is lower in the aorta where shear rate is high, and higher in the arterioles where shear rate is low. Studies of samples of blood of varying hematocrits demonstrate, as is well known, that viscosity falls as hematocrit falls; however, the flow-dependent (shear-thinning) properties of whole blood persist at very low hematocrit values. It has been shown that the cellular concentration at the vessel wall is less than that of the whole fluid. This thin layer of fluid in larger vessels has no significant hemodynamic effect upon blood viscosity. Viscosity values in the arterioles and capillaries are predominantly determined by the flow properties of plasma itself. Plasma also is shown to be flow dependent.

Electrocardiographic Changes in Pregnancy

Nanette Kass Wenger, V. Nelle Strozier, and J. Willis Hurst, Atlanta, Georgia

It has been stated that relatively predictable electrocardiographic changes occur during pregnancy. Several authors describe a leftward shift of the electrical axis of the QRS complex as the pregnancy progresses, with the vector returning toward the normal position prior to delivery. Cardiac dilatation, hypertrophy, displacement, and rotation are among the theories proffered to explain these electrocardiographic changes.

We have studied 24 patients, aged 15 to 37 years, during the course of normal, uncomplicated pregnancies. Twenty-two patients had no cardiovascular symptoms or disease; 1 patient had rheumatic fever in childhood, but there was no clinical evidence of heart disease; 1 patient had rheumatic heart disease with aortic insufficiency, but was completely free of symptoms without cardiac medication.

Beginning in the first trimester, monthly electrocardiograms were recorded for each patient. The postpartum record was used as a "baseline" for comparison. There was no constant or predictable variation in the electrical axis of the QRS complex, the T wave, or the QRS-T angle in any of our patients. These results are compared with the variations seen in the serial electrocardiographic tracings of normal, nonpregnant patients.

Preliminary Study of the Electrocardiogram of the Normal Premature Infant

Nanette Kass Wenger, W. Lorraine Watkins, and J. Willis Hurst, Atlanta, Georgia

With recent advances in diagnostic methods and surgical therapy for cardiac disease, cardiologists are now asked to evaluate younger and younger patients, even in the premature-infant age group. We soon came to realize that normal values had not been established for the electrocardiographic deflections and intervals of the premature infant. This preliminary study was designed to determine the range of normal of the several components of the electrocardiogram of the normal premature infant, in order to make possible differentiation of the pathologic from the normal record.

A preliminary study was carried out on 7 normal premature infants, with a total of 113 serial electrocardiograms available for analysis. Comparing our data on these normal premature infants with those for the full-term infant, some similarity was seen; however, distinct differences were equally apparent. These were seen most particularly as regards P-wave amplitude, range of the QRS electrical axis, amplitude of the QRS complex, incidence and amplitude of Q waves, and incidence and degree of S-T segment deviation. Possible etiologic explanations are offered for these results.

Principles of Management in Surgery of the Hemophiliac

Sigmund A. Wesolowski, Herbert C. Lichtman, and Philip N. Sawyer, Brooklyn, New York

The management of 2 hemophiliacs, each with an infected femoral fracture hematoma, taught us several principles of hemophiliac surgery. Open mid-thigh amputation for a massive infected hematoma was performed in the first case; postoperative bleeding was controlled, but the patient died of proximal infection.

A more radical approach was taken in the second case: a 14-year-old boy hemophiliac with repeated fracture of the left femur, an infected hematoma of the left thigh having a girth of 37 inches, and

septicemia. We embarked upon a course of surgical management which began with an emergency incision and drainage of the left thigh and culminated with elective revision and plastic repair of skin flaps to close the site of disarticulation. A number of problems were successfully overcome: infection and septicemia; postoperative bleeding from large, open, infected wounds; fastness to both blood and plasma transfusions; and the timing of the various surgical procedures. The report presents the details of management as they relate to success: use of fresh blood and fresh plasma transfusions; antibiotic, steroid, and antihistamine therapy; the details of surgical technic including the utility of the ligature, alternating-current electrodesiccation, and our newly developed technic of direct-current electrocoagulation in providing hemostasis in infected, clean, granulation, and scar tissues; and the local management of open wounds in the hemophiliac.

As a result of our experience, we have evolved certain principles of management which promise to allow safe surgery in patients with hemophilia and other hemorrhagiparous states.

Cinefluorographic Studies of Clinical and Hemodynamic Significance of Pulmonary-Artery Pulsations

Robert E. Whalen, James J. Morris, Jr., Rafael R. Hernandez, Edward S. Orgain, and Henry D. McIntosh, Durham, North Carolina

Recognition of pulsations of the secondary branches of the pulmonary artery (PA) is helpful in evaluating patients with heart disease. Cinefluorograms of the right lower pulmonary-artery branches of 120 patients (80 without overt heart disease) were repeatedly studied.

Twelve of 13 patients with atrial septal defect (ASD) pulsated. The exception had stenosis of the right PA, but pulsated in the left PA. All had normal or slightly elevated PA pressures, increased pulmonary flow, and increased systolic input into the PA. Unexpectedly, 4 of 5 patients studied after correction of their ASD still pulsated. One of 14 patients with rheumatic heart disease with an elevated PA pressure, and 1 of 5 patients with patent ductus arteriosus (PDA) with increased pulmonary flow pulsated. Fourteen (8 diabetics) of 80 patients without heart disease pulsated.

Studies on 6 normal dogs revealed that balloon occlusion of 1 PA produced doubling of systolic input, no change in pressure, and pulsations of the unoccluded PA. Injection of hypertonic saline into the PA produced marked increase in PA pressure and decrease in pulmonary flow, but *no* pulsations.

The data from the ASD, rheumatic heart disease, and animal groups indicate that PA pulsations are independent of PA pressure and arteriolar resistance and are a function of systolic input into the PA. The increased flow in patients with PDA, unlike those with ASD, is distributed throughout systole and diastole. The presence of pulsations in corrected ASD and diabetics suggests that alterations of vessel wall elasticity may be operative.

Fever, Splenomegaly, and Atypical Lymphocytes: A Syndrome Observed Following Cardiac Surgery Utilizing a Pump Oxygenator (P)

Edwin O. Wheeler, John D. Turner, and J. Gordon Scannell, Boston, Massachusetts

During the past year, among 54 patients undergoing open-heart surgery utilizing total cardiopulmonary bypass, we have observed 6 cases of a syndrome characterized by fever, splenomegaly, and atypical lymphocytes.

Signs of this disorder were first recognized 3 to 7 weeks after operation. Fever was found in 4 of the 6 patients, while all had splenomegaly and atypical lymphocytes. The fever did not exceed 102 F., but lasted 7 to 21 days; atypical lymphocytes were present for as long as 2 months and splenomegaly persisted for 1 to 12 months. Hepatomegaly was present in 3 patients, but only minor, inconstant abnormalities in liver function were found. Blood cultures and heterophil agglutinations were negative. The course in all 6 patients was benign and no specific therapy was given.

The white count varied from 5,200 to 11,200 with 44 per cent to 68 per cent lymphocytes. Atypical lymphocytes (viral cells, Downey cells type III, Türk cells) made up 10 per cent to 28 per cent of the white cells, except in 1 patient who had only a few.

The incidence of this syndrome is probably higher than the 11 per cent we observed, since not all 54 patients were closely followed by us after discharge from the hospital. Its cause is not known. To date, it has not been reported following closed cardiac surgery or multiple transfusions. The absence of chest pain, pleuritis, pericarditis, or arthritis clearly differentiates it from the postcommissurotomy syndrome. A viral etiology has been suspected, but no evidence to support this has yet been found.

Incorporation of Acetate Into Fatty Acid and Cholesterol by Normal and Atherosclerotic Intima (P)

Arthur F. Whereat, Philadelphia, Pennsylvania

It has been demonstrated that there is an increased consumption of oxygen by aortic intima from rabbits rendered atherosclerotic by choles-

terol feeding when compared with aortic samples from control rabbits. This difference in oxygen utilization parallels the severity of the atherosclerosis when 3 portions (arch, thoracic, and abdominal) from the same aorta are studied simultaneously.

In pursuit of an explanation for this difference in oxygen demand by the atherosclerotic intima, rates of incorporation of labeled acetate into cholesterol and fatty acids have been studied. It has been found that the rates of synthesis of cholesterol from acetate were not much different when intimal samples from atherosclerotic and control animals were compared. In marked contrast, the incorporation of acetate into fatty acids was very small in the control intima, but greatly increased in the atherosclerotic intima. Incorporation of acetate into fatty acids in the atherosclerotic intima was increased when expressed as specific activity (counts/min./mg. fatty acid). Moreover, the fatty-acid content of the atherosclerotic intima is greater than that of the control intima, so that this incorporation reflects an even greater "turnover." It has also been observed that succinate included in the medium stimulates the incorporation of labeled acetate into fatty acids.

These studies bear upon the controversy as to whether passive deposition or synthesis is responsible for the accumulation of lipid within vascular intima.

Idiopathic Ventricular Septal Hypertrophy (Muscular Subaortic Stenosis) and Its Differentiation from Discrete Valvular and Subvalvular Aortic Stenosis

E. Douglas Wigle, Raymond O. Heimbecker, and Ramsay W. Gunton, Toronto, Canada

Fifteen cases of the condition "muscular subaortic stenosis" have been studied, 10 of them intensively by clinical, hemodynamic, and angiocardiographic means. In 4 cases, surgical and/or postmortem observations are available. In these cases, the fundamental abnormality, judging from angiographic, surgical, and postmortem observations, has been massive hypertrophy of the interventricular septum which frequently leads to right, as well as left, ventricular outflow tract obstruction. In addition, there is impaired ventricular filling in diastole, resulting in prominent *a* waves in the jugular venous pulse and right atrial pressure trace and a loud, often palpable, left atrial gallop sound.

Elevation of end-diastolic pressure in both ventricles in the presence of usually normal cardiac outputs implies a decreased distensibility or compliance of both ventricles secondary to the septal muscle mass.

In the peripheral arterial pressure traces the shape, the rate of rise of pressure, the systolic upstroke time (to the peak systolic pressure), and the relative heights of the percussion and tidal waves have been studied and compared with those of surgically proven discrete fixed aortic valvular and subvalvular stenosis. It has been found that there are characteristic differences in these features of the peripheral arterial pressure trace that allow differentiation of muscular from the fixed or discrete varieties of aortic stenosis.

A unique clinical, hemodynamic, and angiographic picture results from this muscle mass in the ventricular septum that obstructs the outflow of blood from both ventricles and impairs their diastolic filling.

The Coronary Care Unit: A New Approach to Treatment of Acute Coronary Occlusion

Morris Wilburne, Beverly Hills, California

Sudden death due to cardiac arrest in patients convalescing uneventfully from acute myocardial infarction, often minimal, is an ever-present threat. Recent autopsy experience with sudden death due to coronary disease indicates that perhaps as many as two-thirds are reversible. Further, evidence is accumulating suggesting that at least one-fourth of cardiac arrests due to myocardial infarction are successfully resuscitated by combined closed-chest cardiac compression and pulmonary ventilation.

A cardiac-care program is presented that is designed to prevent irreversible death due to cardiac arrest in the hospitalized patient with acute coronary disease. The program involves the institution of a central Coronary Care Unit to which all patients with acute coronary disease are assigned. A central, multichannel, physiologic monitoring system is described in which a continuous, simultaneous oscilloscopic electrocardiogram and digital readout of arterial pressure or pulse volume is displayed. Other parameters may be obtained. Each patient's room or cubicle has an individual, wall-mounted, duplicate display panel, with an outlet defibrillator connection. An alarm buzzer is sounded should ventricular fibrillation or cardiac asystole develop. The nurses' station is equipped with a mobile cart carrying a 440-volt external defibrillator, an external cardiac pacemaker, cardiac resuscitative drugs, and other equipment described in the text.

The Coronary Care Unit is under continuous supervision of a physician or a specially trained nurse capable of recognizing ventricular fibrillation and ventricular standstill. The Unit is supplemented by additional personnel trained in cardiac resuscitation and qualified to administer immediate closed-chest cardiac massage and mouth-to-mouth or mouth-to-airway ventilation. An organized program and step-by-step plan of resuscitation is described.

Effect of Sudden Reduction in Impedance on Left Ventricular Performance

David E. L. Wilcken, Abraham Guz, Andre A. Charlier, Louis C. Zanger, and Ronald J. Stoney, San Francisco, California

The effect on left ventricular performance of sudden reduction in impedance to left ventricular outflow was studied in dogs. Modified Kolin sine-wave flow transducers were implanted at the root of the aorta at least 1 week before the study. Impedance was reduced suddenly by: (1) injections of nitroglycerine and acetylcholine into the ascending aorta; and (2) abrupt opening of a previously implanted arterial graft which led from the abdominal aorta to a subcutaneous pouch. The blind end of the graft was opened to atmospheric pressure for 1 or 2 heart beats and then clamped.

In 25 experiments on 5 dogs, the drug injections decreased mean arterial pressure 10 to 20 mm. Hg during the 4 to 5 beats before tachycardia began. There was no alteration in stroke volume, peak velocity, or acceleration during this time.

Reduction in impedance by rapid bleeding decreased mean arterial pressure by 20 to 30 mm. Hg between successive beats. This was accompanied uniformly by an increase of 24 to 42 per cent (7 to 12 ml.) in the left ventricular stroke volume of the next beat. The peak velocity also increased, but there was no change in the acceleration of the ejected blood. Similar changes occurred in the same beat when the reduction in impedance occurred in early systole.

We conclude that stroke volume and peak velocity increase in the next beat when abrupt and large reductions in impedance are produced.

Effect of Extracorporeal Circulation on Digitalis

Vallee L. Willman, Theodore Cooper, and C. Rollins Hanlon, St. Louis, Missouri

Among the factors which determine postoperative digitalis requirements of patients subjected to open-heart surgery are the effects of extracorporeal circulation. This intervention may alter the need for digitalis or may alter the quantity of usable agent stored in the body.

The dosage of a rapidly acting glycoside which would produce nodal tachycardia was determined for 15 dogs, 10 of which were chronically digitalized with digitoxin. When toxicity could be repeatedly reproduced by comparable amounts of glycoside, the animals were subjected to the surgical procedures involved in 30 minutes of cardiopulmonary bypass. The tolerance to digitalis was reassessed in the early postoperative period and at subsequent intervals in survivors.

The experimental results indicated: (1) In undigitalized dogs, the dosage of digitalis required to produce nodal tachycardia following extracorporeal circulation was essentially the same as for the normal control state (0.07 to 0.08 mg./Kg. ouabain). (2) In chronically digitalized dogs, the tolerance to the digitalis challenge was increased by 30 minutes of total body perfusion (0.025 to 0.035 mg./Kg.—control; 0.05 to 0.06 mg./Kg.—after perfusion). (3) The control tolerance values were reproducible whether the animals were anesthetized with thiopental sodium or were unanesthetized. (4) Thoracotomy and dissection without perfusion also increased the tolerance to digitalis. (5) There was no significant elevation or alteration in serum potassium during any experiment. However, blood catecholamine levels were consistently elevated (8 to 19 μg./L.).

Acute Constrictive Epicarditis Following Idiopathic Pericarditis

Donald R. Wilson and Susan M. Lenkei, Toronto, Canada

The early development of severe constriction with impairment of diastolic filling and marked reduction in cardiac output has been observed in 5 patients who developed constrictive epicarditis a few months after the onset of acute pericarditis. In 1, infectious mononucleosis was the proven etiologic agent, while the others fell into the idiopathic group.

The early occurrence of right-sided congestive heart failure during an attack of acute pericarditis was one of the diagnostic features. Investigation included intra- and extracardiac phonocardiograms, characteristic pressure tracings, and repeated cardiac-output estimations. Two of the patients developed pericardial tamponade, but, with repeated pericardiocentesis, little improvement was noted because of the underlying constrictive layer. One case developed secondary hyperaldosteronism.

At operation, although the parietal pericardium was involved, the true constriction was due to a thickened adherent epicardium. With removal of the epicardium, there was immediate improvement of the venous obstruction and increased cardiac output. The left and right ventricles were cleared, in that order, but no attempt was made to clear the right side of the heart. Pathologic studies showed generalized fibrosis, but no specific etiologic factor. The follow-up has been gratifying.

Acute Effects of α-Methyl Dopa in Thyrotoxic Patients and Normal Subjects (P)

William R. Wilson, Faruk J. Tutunji, and Ernest O. Theilen, Iowa City, Iowa

Some manifestations of hyperthyroidism have been ascribed to the effects of catecholamines. Five thyrotoxic patients and 5 normal subjects were given α-methyl dopa to test this hypothesis. This drug may be an inhibitor of a decarboxylase necessary for the transformation of dopa to dopamine, a precursor of catecholamines. Amounts used in this study (0.7 Gm./M.^{2}, intravenously) produce lowered supine arterial pressure and cardiac output in hypertensive patients. Triplicate observations were made before, and 3 hours after, the drug. Pulse rate decreased from 120 to 106 beats/min. ($P < 0.02$) in the thyrotoxic patients and from 69 to 63 ($P < 0.05$) in the normal subjects. There was no appreciable change of cardiac index in either group (thyrotoxic patients, 5.4 to 5.2 L., and controls 3.0 to 2.6 L.). Stroke index increased slightly in the thyrotoxic group (45 to 49 ml., $P < 0.05$) and decreased in the controls (43 to 41 ml.). Mean supine arterial pressure was not changed in the thyrotoxic patients (95 to 91 mm. Hg), and was reduced slightly in the controls (88 to 79 mm. Hg, $P < 0.01$). Total systemic resistance and oxygen consumption did not change in the 10 subjects.

Normal and thyrotoxic patients did not respond to α-methyl dopa with decreased arterial pressure and flow as hypertensive patients do. If α-methyl dopa does inhibit the formation of norepinephrine, our studies indicate that most of the hemodynamic effects of thyrotoxicosis are not due to an excess of catecholamines. Increased sensitivity to these substances may be an important mechanism.

Effects of an Aldosterone Antagonist and a Benzothiadiazine Individually and in Combination in Benign Hypertension

Bertram M. Winer, Boston, Massachusetts

The basal blood pressure, the blood pressure responses to intravenously infused trimethapan, norepinephrine, and angiotensin II, 24-hour exchangeable sodium, plasma volume, body weight, and serum electrolytes were determined during oral administration of a placebo, spironolactone (400 mg. daily for a month), hydrochlorothiazide (150 mg. daily for a month), and both diuretics in a group of 11 patients with benign hypertension.

Basal blood pressure averaged 191/106 mm. Hg during the placebo, 167/98 during spironolactone, 166/97 during hydrochlorothiazide, and 148/91 during both. Responses to trimethapan averaged 167/101 during placebo, 141/89 during spironolactone, 142/92 during hydrochlorothiazide, 119/78 during both. The responses to norepinephrine and also to angiotensin II followed a similar pattern. The differences between the placebo and either diuretic, and between either diuretic and the combined diuretics were statistically significant.

Exchangeable sodium was significantly decreased by each diuretic. The decreases in exchangeable sodium after spironolactone and after combined diuretic therapy were similar, and were significantly greater than after hydrochlorothiazide. Plasma volume and body weight were reduced by each diuretic; the decreases were greater when the diuretics were combined. Effects on serum sodium were small. Serum potassium levels fell significantly during hydrochlorothiazide and were slightly above control values during spironolactone or combined diuretic therapy.

It is concluded that an aldosterone antagonist and a benzothiadiazine have equivalent antihypertensive activity in benign hypertension. Together they provide an additive antihypertensive effect without a hypokalemic effect. Their combined use represents an advance in the therapeutics of hypertension.

Differential Characteristics of Certain Arrhythmias by Direct-Body, High-Frequency Ballistocardiography

Nahum J. Winer, New York, New York

To date, no differential dynamic characterization of arrhythmias has been attainable by ballistocardiography. High-frequency, direct-body ballistocardiography attains a sensitivity that does this with the aid of heart-sound correlation for accurate wave notation. Four factors underlie dynamic behavior:

1. Respiratory phase and resulting degree of cardiac filling determining the amplitude of an abnormal beat. This can be stabilized by suspended midinspiration.

2. Period of diastolic filling: the earlier the abnormal beat, the more depressed the amplitude and abnormal the configuration; conversely, the compensatory beat.

3. Pathway of ventricular excitation: impulses of atrial or nodal origin that follow a normal pathway maintain a normal interventricular relationship, producing a good HI downstroke regardless of prematurity; intraventricular impulses produce greater asynchrony or excitation and HIJ dissociation.

4. Myocardial tone: in the "low-reserve" heart, the initial downstroke may show deterioration even when of atrial origin and only slight prematurity.

Our studies demonstrate: (1) good HI downstrokes in "high-reserve" hearts in premature atrial beats—of sinoatrial or coronary-sinus origin, and atrial fibrillation. These contrast with poor HI downstroke and overall deterioration in "low-reserve" hearts. (2) Discrete H_R-H_L-J_R dissociation in premature ventricular beats. Deep J_R-J_L segmentation may follow in "low-reserve" hearts. (3) Interpolated ventricular contractions, studied

in a case of left ventricular origin, repetitively, form 5 pattern groups: H_L-H_R and overall dissociation of the interpolated beat; dominant H_L downstroke in the first versus H_R downstroke in the third beat; poor HI and J_R-J_L segmentation of the fourth beat correlated with shorter R-R interval; normal fifth—like first—beat.

Further Experience with High-Frequency, Direct-Body Ballistocardiography in Early Myocardial Infarction

Nahum J. Winer, New York, New York

Early diagnosis of myocardial infarction remains an urgent challenge. Further experience with qualitative high-frequency, direct-body ballistocardiography supports observations that: (1) alteration in myocardial dynamics is greatest in early infarction when that of the electrical impulse may be absent or delayed; (2) acceleration of the initial phase of systole best reflects the myocardial state; (3) this method best achieves the necessary sensitivity since its acceleration approximates the second derivative of the Starr high-frequency table and ultra-low-frequency acceleration, and the cut-off in sensitivity below natural body frequency may advantageously exclude possible attenuation of the higher-frequency aberrations being sought; (4) heart sounds offer more valid correlation than the electrocardiogram for accurate wave notation; (5) suspended midinspiration minimizes the artifactual effects of "splanchnic pooling"; and (6) head-foot direction is apparently adequate.

Characteristic alterations observed were: (1) dissociation of a normally monopeaked HI correlated with the third component of the first sound into depressed H_R-H_L segments correlated with the first and fourth components, respectively; (2) J_R is often accentuated as may be antecedent H_{IC}; and (3) diminution in amplitude may extend to the overall complex.

The slides demonstrate 3 functional principles: correction of "deterioration" by suspended midinspiration; higher-frequency acceleration belying the apparent HI "deterioration" of displacement; and improved HI in the stronger versus weaker beat in pulsus alternans. They also show 7 examples of alterations in early myocardial infarction —6 with nonspecific electrocardiographic changes —all substantiated by other laboratory methods, and 3 subsequently confirmed electrocardiographically. Patterns were all restored to normal with recovery.

In Vitro Degradation of Angiotensin II-^{131} in Normotensive and Hypertensive Human Sera (P)

Robert L. Wolf, Milton Mendlowitz, Stanley Gitlow, and Eric Naftchi, New York, New York

Mixtures of sera either from patients with untreated primary hypertension or from normotensive subjects and varying quantities of angiotensin II-I^{131} were incubated in vitro. The solution was analyzed by radiochromatoelectrophoresis after the proteins were stained with bromophenol blue. The radioactivity of the substances on the strips was assayed in an automatic strip scanner using a thin-window gas flow counter, and the mobility of these substances was compared with that of unaltered angiotensin II-I^{131}. Two separate peaks of radioactivity were present in the mixtures, and by measurement of the areas beneath these peaks, the amounts of unaltered angiotensin II-I^{131} (with the slower mobility) and the angiotensin II-I^{131} degradation components (with the faster mobility) were determined and the per cent angiotensin II-I^{131} degraded was calculated.

The per cent angiotensin II-I^{131} degraded was approximately 2-fold greater in the primary untreated hypertensive subjects than in the normotensive control patients. Two patients with secondary renal hypertension had percentages of angiotensin II-I^{131} degraded within the normotensive range. In patients with primary untreated hypertension, the occurrence of a relatively slow in vivo angiotensin II-I^{131} turnover rate and the relatively large per cent angiotensin II-I^{131} degraded in vitro indicates that the degradation of angiotensin II in blood and tissues is not the same, and suggests the existence and importance of extravascular factors in angiotensin II-I^{131} metabolism. This in vitro technic may provide a simple, rapid, radiochemical distinction between normotensive, primary hypertensive, and secondary renal hypertensive subjects.

Changing Spectrum of Bacterial Endocarditis: 100 Cases in the Era of Antibiotics and Cardiac Surgery

Charles F. Wooley and Don M. Hosier, Columbus, Ohio

Antibiotic therapy, cardiac surgery, and diagnostic procedures have altered the classic concepts of bacterial endocarditis. The differences noted are deemed worthy of report.

Patients with congenital heart disease form 29 per cent of this series. However, these 29 patients are a small fraction of 1,400 cases of proven congenital heart disease, supporting impressions that bacterial endocarditis is an infrequent complication of congenital heart disease and suggesting that earlier autopsy studies overemphasized this association.

Contrary to some concepts, 6 patients with rheumatic heart disease and bacterial endocarditis had severe mitral stenosis. Twenty-four patients were under 12 years of age, and 16 were over 60, emphasizing the relative frequency of the disease

in these age groups. Alpha streptococci occurred only 30 times, while staphylococci, antibiotic-induced negative blood cultures, and miscellaneous organisms accounted for 56 cases.

The intimate relationship between cardiovascular surgery and bacterial endocarditis is emphasized. Cure of endocarditis and subsequent surgical correction of the basic cardiac defect occurred in 9 patients. Endocarditis followed cardiac surgery in 8 others; this clinical form of endocarditis simulates experimental endocarditis and emphasizes the unresolved problem of antibiotic usage at the time of cardiac surgery. Catastrophic consequences of bacterial endocarditis (valve perforations, A-V fistula, saddle embolus, arterial aneurysms) were indications for surgery in 5 patients.

Immediate survival (all cases, all organisms) was 60 per cent. Forty-two patients are living and well, with 21 patients followed longer than 5 years, 6 longer than 10 years. Long-term prognosis was best in the group with congenital heart disease.

Pregnancy and Congenital Heart Disease

Charles F. Wooley, Vincent Runco, Hugh S. Levin, and Joseph M. Ryan, Columbus, Ohio

Two hundred and eighty-four pregnancies complicating congenital heart disease in 103 women form the basis for this study. In 80 women, the diagnosis of the cardiac defect was based on catheterization data or surgical findings, and on substantial clinical evidence in 23.

Thirty-one patients had atrial septal defects, 27 patent ductus arteriosus, and 23 ventricular septal defects. Other defects were: pulmonic stenosis (5), tetralogy of Fallot (5), coarctation (4), Ebstein's (3), aortic-valve lesions (3), and unclassified (2).

One maternal death occurred, staphylococcal endocarditis following dental extraction during pregnancy. There were 61 fetal losses in the 284 pregnancies; 48 were spontaneous abortions. The spontaneous-abortion rate of 17 per cent differs little from an unselected pregnant group. Perinatal mortality was average for this hospital.

There was an apparent correlation between fetal loss and maternal pulmonary hypertension or cyanosis. The 54 patients with atrial or ventricular septal defects had 172 pregnancies with 41 fetal losses. Within this group, the 18 patients with pulmonary hypertension accounted for one-half the fetal mortality, with only one-third of the total pregnancies. The cyanotic group had 11 fetal losses in 21 pregnancies. There were no cases of bacterial endocarditis in the postpartum or postabortal period in 284 pregnancies.

This study indicates that many women with congenital heart disease have sustained multiple pregnancies without incident. Favorable maternal prognosis and fetal survival in this nonoperated series suggests that the effect of pregnancy on congenital heart disease is not sufficient indication for cardiac surgery in the gravid state.

Peripheral Arterial Embolism (P)

Jess R. Young, Victor G. deWolfe, Alfred W. Humphries, and Fay A. LeFevre, Cleveland, Ohio

The management of 102 patients with 118 peripheral emboli involving 145 limbs is described. The heart was the source of 103 emboli. Atrial fibrillation was present in 60 per cent of the patients.

Embolectomy was performed for all nongangrenous limbs with persistent, severe ischemia resistant to conservative therapy. It was attempted for 71 of the 118 emboli. Embolectomy was not done for limbs with mild ischemia or with irreversible gangrene and 83 per cent of these limbs survived. In those limbs with severe ischemia, 85 per cent survived with embolectomy. Limb survival rate was 90 per cent when embolectomy was performed within 12 hours of embolism, 81 per cent when performed in the 12- to 48-hour period, and 64 per cent in the 2- to 7-day period. The overall mortality rate was 25 per cent. There have been no further emboli and only 1 death in a group of 23 patients who have had combined embolectomy, mitral commissurotomy, and atrial appendectomy.

Contrary to the widely held opinion that embolectomy must be done within 10 to 12 hours of embolism, we have found that the setting of an arbitrary time limit is unjustifiable. On the contrary, prompt embolectomy should be performed on all nongangrenous limbs showing persistent signs of severe ischemia regardless of the time interval following embolism.

Embolectomy should be combined with an intensive medical and surgical attack of the source of the embolus. If the source cannot be eliminated, long-term anticoagulation is indicated.

Prognostic Significance of the Magnitude of S-T Segment Shift in Myocardial Infarction (P)

Rudolf Zalter and Elie Y. Sadik, Chicago, Illinois

The poor prognosis associated with marked S-T deviation in acute myocardial infarction has often been noted. To evaluate the validity of this impression, the consecutive electrocardiographic files of 15,000 patients, covering a 3-year period, were screened for S-T segment shift. An S-T (J junction) deviation of 4 mm. or more in any of the

12 conventional leads formed the basis for inclusion in the present study. The case histories of these patients were then reviewed and analyzed. Eighty-one cases with S-T deviation (elevation or reciprocal depression) of 4 mm. or more were found. Of these, 49 (60.4 per cent) died during initial hospitalization; 77.4 per cent of these deaths occurred within 48 hours after the electrocardiogram was recorded. Of the 81 cases, there were 28 cases with S-T deviation of 7 to 15 mm., 22 of which (78.6 per cent) died. Of the remaining 53 cases with an S-T deviation of 4 to 6.9 mm., 26 (49 per cent) died. For comparison, 53 consecutive cases of acute myocardial infarction with S-T deviation of 0 to 4 mm. were similarly reviewed. The mortality in this group was 26.4 per cent. The difference in mortality (60.4 per cent vs. 26.4 per cent) between the 2 groups was statistically significant (chi-square analysis, $P < 0.001$). It is concluded that S-T deviation of 4 mm. or more in any of the 12 conventional electrocardiographic leads carries a poor immediate prognosis, which is particularly grave if the S-T deviation is 7 mm. or more.

Surgical Therapy of Acute and Chronic Pericardial Disease

Robert Zeppa and Richard M. Peters, Chapel Hill, North Carolina

Twenty-nine patients have undergone surgery for pericardial disease in the North Carolina Memorial Hospital since 1952. There were 19 cases of chronic constrictive pericarditis; 12 of these were due to tuberculosis. There was 1 case of pericardial nocardiosis; 4 cases were of uncertain etiology, and 1 followed a hemopericardium after trauma. The constricting scar was confined to the right heart in 2 cases. Ten cases of pericardial effusion were treated by partial resection of the pericardium and closed-chest drainage. Three deaths occurred; all of these patients had severe constriction and were in the over-50 age group. The studies have included cardiac catheterization preoperatively in 14 patients and postoperatively in 4. Angiocardiography was performed 5 times.

From our clinical, physiologic, microbiologic, and pathologic studies, the following conclusions were reached: (1) digitalis therapy for the sick and constricted myocardium is mandatory; (2) early surgical drainage during the stage of effusion prevents the development of a constricting scar and associated myocardial injury; (3) the postoperative mortality and morbidity in patients with constriction is favorably influenced by midline sternotomy, careful correction of fluid electrolyte and protein losses, and early recognition and vigorous treatment of respiratory decompensation; (4) antituberculous therapy begun during the stage of effusion does not prevent the evolution of scar from fluid; and (5) removal of the scar from the ventricles has been adequate in these cases.

Experiences with Atrial Flutter in Infants and Children

Robert F. Ziegler, Detroit, Michigan

Paroxysmal atrial flutter has been observed in infancy and childhood with a greater frequency than previously reported; in fact, it has been one of the most frequent mechanisms of ectopic tachycardia in the infants of this series. While it has been observed in a wide variety of congenital malformations, it has occurred most often with an otherwise normal heart.

This form of tachycardia has been observed most commonly in the early neonatal period and has usually not been recurrent, even without prophylactic drug administration. Conversion to normal sinus rhythm has usually occurred with full digitalization, quinidine seldom being necessary. In a few cases the atrial flutter has proved refractory to all forms of treatment, but even in these instances it has been well tolerated clinically. In 1 case, conversion to normal sinus rhythm occurred spontaneously after 4½ years of continuous flutter. There have been no fatalities even with associated, severe congenital malformations, including both spontaneous and catheter-induced flutter in interventricular septal defect, subendocardial fibroelastosis, and Ebstein malformation of the tricuspid valve.

During normal sinus rhythm, babies with flutter have displayed typical, "nonspecific" P-wave abnormalities in the precordial leads, regression of which to normal coincided with the subsidence of recurrent attacks. These P-wave abnormalities are analyzed and illustrated from amplified, simultaneous precordial-lead, serial electrocardiograms.

Importance of Amplification Technics in Routine Clinical Electrocardiography (P)

Robert F. Ziegler, Detroit, Michigan

Although not new, amplification technics for scalar electrocardiography have apparently not been utilized on any routine basis. This study reports the specific clinical contributions of multiple precordial leads recorded routinely with the following technical adjuncts: (1) simultaneous lead system; (2) fast camera speed; and (3) 3 × amplification, using an electronic amplifier coupled to a galvanometer string which was kept at 1 N sensitivity in order to minimize distortion. The chief advantage resides in the type of information gained from the undistorted magnification of small voltage deflections, such as the separate elements

of the P wave and the initial QRS forces representative of interventricular septal activation.

This technic, from the morphology of the amplified P wave, has made possible the earlier and more accurate detection of minimal atrial enlargement, as well as a more accurate evaluation of relative size when the atrial enlargement is of marked degree or of combined type. Another important differentiation made possible by this technic is that of a true Q wave (on either side of the precordium) from an apparently initial negative deflection which is actually preceded by either an isoelectric segment of QRS or a small, otherwise unrecognized, initial upward deflection. This differentiation, along with hemodynamic and anatomic correlations, has contributed, in turn, to a better distinction between bundle-branch block and hypertrophy (plus dilatation) patterns.

Precordial Lead P-Wave Patterns in Atrial Enlargement

Robert F. Ziegler, Detroit, Michigan

With amplified simultaneous leads, the form of the normal P-wave pattern is first analyzed in terms of predominantly right and left atrial components, as observed particularly in leads from respective sides of the precordium. Modifications of these patterns, principally in terms of increased voltage of the respective components, are next related to those hemodynamic or anatomic situations in which there is increased work or size of either right or left (or both) atrium. The diagnostic accuracy of the criteria developed and illustrated in this study has proved to be superior to any other clinical method, including conventional radiography.

Important clinical applications include the following: (1) differential diagnosis, where specific atrial enlargement is important; (2) quantitation of the degree of atrial enlargement; (3) clinical evaluation of specific hemodynamics, such as determination of factors of flow versus resistance in the genesis of pulmonary artery hypertension; (4) clarification of problems related to cardiac position: rotation, displacement, dextrocardia, etc.; and (5) diagnostic and prognostic evaluation of atrial arrhythmias.

Use of Methoxamine in Treatment of Paroxysmal Supraventricular Tachycardia

Walter T. Zimdahl, Buffalo, New York

Methoxamine is a new synthetic sympathomimetic compound which differs from epinephrine primarily in having methoxy instead of hydroxy groups in the benzene ring. It has been reported that the drug produces a potent and sustained pressor response in experimental animals. We wish to call attention to the use of this drug in the treatment of paroxysmal supraventricular tachycardia. Not only is this drug effective in arresting the tachycardia, but because of its powerful pressor action, it is especially useful in cases complicated by vascular collapse of frequent occurrence. We have used the drug now in 30 patients for the treatment of paroxysmal supraventricular tachycardia. We have found that the drug acts almost immediately. The side actions have been minimal. The use of the drug also eliminates the necessity for giving intravenous digitalis, waiting around for quinidine or pronestyl to act.

Four cases of paroxysmal supraventricular tachycardia complicated by vascular collapse and successfully treated by this agent have been reported; 2 of our cases represent such an incident. One patient, a 43-year-old male with frequent attacks of paroxysmal tachycardia and severe vascular collapse would require emergency treatment in the hospital for several days. After use of methoxamine, the attacks aborted quickly and no further collapse occurred. Another patient with idiopathic tachycardia has been successfully treated 75 times during 76 attacks in the past 2 years.

Our experimental studies have suggested a direct myocardial effect, as well as a vagal effect, of the drug. It is felt that methoxamine is the treatment of choice in this syndrome.

Effect of Exercise on Cerebral Blood Flow (P)

Eldred G. Zobl, Frederick N. Talmers, and Lesem J. Baer, Dearborn, Michigan

A study was made of the relation of cerebral blood flow and cerebral vascular resistance to cardiac index and brachial-artery pressure at rest and during exercise in 13 normal and 7 hypertensive patients. The left internal jugular vein was catheterized by passing a cardiac catheter from a left arm vein and lodging the tip of the catheter in the internal jugular vein inside the cranial vault. A separate catheter was passed into the right atrium, and the brachial artery was cannulated with a Cournand needle. At rest and during exercise, simultaneous measurements were made of the cerebral blood flow by the nitrous-oxide method, of cardiac output by the Fick method, and of brachial-artery pressure. The mean cerebral blood flow at rest in the normal patients was 52.46 cc./min./100 Gm. and in the hypertensive patients 46.27 cc./min./100 Gm. ($P < 0.02$). The cerebral resistance was 1.71 and 2.37 mm. Hg/ml. blood/100 Gm./min., respectively. In both groups, the cerebral blood flow increased slightly after exercise, but not in proportion to the average 3-fold

increase in cardiac index. The cerebral vascular resistance did not change, although the total peripheral resistance decreased to less than half the resting value. The small increase in cerebral flow in both normal and hypertensive patients was related directly to the increase in mean brachial-artery pressure effected by exercise.

Termination of Refractory Tachycardia by External Electric Countershock (P)

Paul M. Zoll, Arthur J. Linenthal, and M. D. Phelps, Jr., Boston, Massachusetts

Ventricular or supraventricular tachycardia is occasionally refractory to drug therapy and may culminate in congestive heart failure, circulatory collapse, or ventricular fibrillation. The clinical value of external electric countershock has been established for the emergency termination of ventricular fibrillation or tachycardia in the unconscious patient in circulatory arrest without the need for thoracotomy. We have also terminated atrial tachycardia and fibrillation in animals by this technic.

Recently, external electric countershock has been used to terminate refractory tachycardia in 4 patients who were desperately ill with shock and increasing congestive failure, but were not in circulatory arrest. These patients were all men with old or acute myocardial infarctions; 3 were receiving digitalis. The tachycardias were regular, rapid (175 to 240 per minute), and showed bizarre QRS complexes, but could not be definitively localized. The tachycardias were refractory to antiarrhythmic drugs, and after 2, 6, 14, and 22 days, they were terminated immediately under general anesthesia by external electric countershocks of 250 to 450 volts. In 1 patient, coexisting atrial fibrillation was also terminated simultaneously. Shock cleared and congestive failure improved; 3 patients recovered completely but the fourth, with the longest tachycardia, died of renal and hepatic failure.

This technic may prove widely useful for terminating all types of refractory tachycardias. It is effective immediately and it appears safe, with no complications other than the need for anesthesia. It may well prove more effective and safer than the heroic doses of drugs that are often used in these desperate situations.

Long-Term Electric Pacemakers for Stokes-Adams Disease

Paul M. Zoll, Leona R. N. Zarsky, Arthur J. Linenthal, and Howard A. Frank, Boston, Massachusetts

Patients with Stokes-Adams disease may be resuscitated from the emergencies of cardiac arrest by external electric stimulation or countershock, but recurrent attacks continue to threaten life. Long-term external stimulation to prevent seizures is not satisfactory because of pain. Myocardial electrodes do permit painless stimulation at low currents with small pacemakers, but initial trials were unsatisfactory because a rising threshold usually made stimulation ineffective within a few weeks.

After extensive experimental studies, we have developed a pacemaker-electrode system for direct long-term cardiac stimulation. With special pure platinum electrodes, Teflon insulation, and a meticulous procedure to avoid tissue reaction at the site of implantation, thresholds for stimulation have remained low in the dog for over 1 year and in patients for over 9 months. Wires traversing the skin, with the risks of infection and breakage, have been avoided by burying a miniature pacemaker subcutaneously. It discharges continuously at a predetermined rate and is powered by batteries that should last 5 years.

In the last 10 months, these units have been implanted in 14 patients from 8 to 70 years of age, with complete success in 9. Instrument failure or wound sepsis has made temporary exteriorization of the pacemaker necessary in 5 patients. Stimulation continues to be effective in preventing seizures in all patients. Other complications, such as cardiac arrest during surgery, pulmonary atelectasis and infection, generalized edema, and mental confusion with fever were of only temporary concern and all patients are now doing well.

Quantitation of Thrombus Growth: Effect of Heparin

Andrew J. Zweifler, Ann Arbor, Michigan

Thrombosis was produced in the external jugular and superficial femoral veins of dogs by subjecting these vessels to a direct current of 5 ma. for 1 hour between 2 small platinum electrodes held in contact with opposite sides of the in situ vein by a molded plastic cuff. Each resulting thrombus was removed, measured, and weighed. To determine the rate of growth, thrombi were either examined immediately after their production or 4 days after thrombogenesis. The ability of heparin to influence the size of the 4-day thrombus was then determined. Heparin was administered either subcutaneously with clotting times controlled at about twice normal levels, or every 8 hours by the intermittent intravenous method.

In the external jugular vein, the average acute

thrombus weighed 48 mg., the average 4-day thrombus weighed 172 mg., and the average 4-day thrombus after heparin therapy weighed 100 mg. In the superficial femoral vein, the average acute thrombus weighed 34 mg., the average 4-day thrombus weighed 254 mg., and the average 4-day thrombus after heparin therapy weighed 100 mg. The statistical significance of the effect of heparin therapy was much greater in the femoral series ($P < 0.01$) than in the external jugular series ($P < 0.2$).

In the untreated dog, small venous thrombi produced by direct current grow considerably over a 4-day period. In the superficial femoral vein this growth is inhibited substantially by heparin therapy, but only occasionally is it stopped completely. These effects of heparin are not nearly so marked in the external jugular vein.

AMERICAN HEART ASSOCIATION

Fifteenth Annual Meeting

COUNCIL ON ARTERIOSCLEROSIS

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THE STUDY OF ARTERIOSCLEROSIS

BAL HARBOUR, MIAMI BEACH, FLORIDA

OCTOBER 18-20, 1961

Abstracts of Papers

(Listed alphabetically by first author)

(P) *Papers presented at the Meeting*

(Abstracts for papers presented on Friday, October 20 are included in Abstracts of the AHA Scientific Sessions)

(A Complete Program of all events is printed separately.)

Treatment of Hypercholesteremia: Comparison of Triparanol and Nicotinic Acid

Richard W. P. Achor, Norman A. Christensen, Kenneth G. Berge, and Harold L. Mason, Rochester, Minn.

Two drugs used clinically to decrease elevated concentrations of cholesterol in the blood are triparanol and nicotinic acid. These 2 agents were studied in 18 patients whose mean pretreatment value for plasma cholesterol was 346 mg. per 100 ml. All patients were seen at monthly intervals, at which time determination of cholesterol (modified Zak method) and other indicated examinations were done.

Nicotinic acid then was given for 9 months. The optimal response for a 3-month period was obtained with a mean daily dose of 4.3 Gm., which produced a mean cholesterol concentration of 235 mg. This was a 29 per cent decrease from the mean value of 332 mg. obtained during a subsequent 3-month period when a placebo was used.

Triparanol then was given in a daily dose of 250 mg. for 3 months, which resulted in a mean cholesterol concentration of 313 mg. (6 per cent less than during use of the placebo). Sixteen of the patients then were given 500 mg. daily for 3 months; the mean cholesterol level decreased to 302 (–9 per cent). Eleven of these 18 patients subsequently received 1,000 mg. per day for another 3-month period, with the concentration of cholesterol decreasing to 310 mg. from a value of 357 mg. (–13 per cent) during a placebo period.

Nicotinic acid produced flushing, nausea and transient abnormalities in tests of hepatic function. These were minor and did not interfere with treatment. Triparanol caused considerable loss of hair in 6 patients, in 1 of whom ichthyosis developed.

Renal Enlargement and Monckeberg Arteriosclerosis After Injections of Hematoporphyrin

Rudolf Altschul, Saskatoon, Saskatchewan, Canada

In rabbits injections of hematoporphyrin have decreased serum cholesterol after 5 to 24 hours to a highly significant degree. When this reaction was tested for prolonged periods on rabbits which received 0.9 Gm. cholesterol daily, there was no significant inhibition of cholesterolemia or atherosclerosis. However these rabbits had unusually large kidneys. Thereupon a series of rabbits were injected repeatedly for 1 to 12 weeks with 0.02 Gm. hematoporphyrin without receiving cholesterol. At autopsy the kidneys were enlarged in the cases treated for more than 2 weeks and in some animals at the end of the first week. The increase in weight over that of control litter mates ranged up to 619 per cent. Microscopic examination shows a great increase of mitoses in cells of the nephron. In animals treated for 2 to 3 months, there is also parenchymal necrosis with calcification. Changes in the aorta resemble, or are identical with, the Mönckeberg type of arteriosclerosis, namely, endothelial hyperplasia and calcification in the media. This calcification is preceded by intense proliferation of the cells between the elastic membranes, followed by cell death and then by disappearance of the necrotic cell bodies. Calcium salts are deposited into, or absorbed by, these cell-free areas and the elastic membranes. Thus, the aortic changes resemble those brought about by epinephrine, ergot, or thyroxin.

Failure of Triparanol to Inhibit Hypercholesterolemia and Atherosclerosis in the Rabbit

Mark L. Armstrong, William E. Connor, and Robert A. Melville, Iowa City, Iowa

Triparanol has been demonstrated to inhibit the biosynthesis of cholesterol in many species. The present study was done to find out whether this effect would influence hypercholesterolemia and atherosclerosis.

Male New Zealand white rabbits were given a diet of Purina chow supplemented with 1 per cent cholesterol and 18 per cent corn oil equivalent to 40 per cent of total calories. Triparanol was added to the diet of one-half of the animals in an amount 0.05 per cent by weight. The other animals were controls. Serum cholesterol was estimated weekly during the first month and monthly thereafter until the animals were autopsied after 3 months. Each aorta was graded 0 to 4 based upon the average atheromatous involvement throughout its length. Scoring was done both on fresh specimens and after sudanophilic staining.

The mean serum cholesterol level for the control group was 45.2 ± 18.1 mg. per cent at the onset of the study and 2,885 ± 1,082 mg. per cent at its termination. The corresponding levels for the triparanol group were 39.0 ± 20.3 mg. per cent and 2,782 ± 605 mg. per cent. The score for aortic atherosclerosis was 1.51 for the controls and 1.73 for the triparanol group. The coronary arteries of both groups showed atheromatous lesions. Both groups had similar reticuloendothelial lipidosis and iris deposits. Food intake and body weights remained similar for each group.

Triparanol did not inhibit hypercholesterolemia and atherosclerosis in rabbits fed a diet containing cholesterol and corn oil.

Hypercholesteremia and Vascular Lesions in Prairie Dogs and Ground Squirrels

Kaye Asdel, Bashir Khan, C. Bruce Taylor, and George E. Cox, Evanston, Ill.

A fat- and cholesterol-rich diet (50 per cent dried egg yolk and 50 per cent vegetable monkey chow) was fed to 18 prairie dogs (genus *Cynomys*) and 18 ground squirrels (genus *Citellus, Tridecinlineatus*) (obtained from Texas via Research Animals, Pittsburgh). Seventeen prairie dogs and 11 ground squirrels survived 12 to 15 months on the yolk diet, then were autopsied. Terminal serum cholesterol levels of the 11 yolk-fed ground squirrels averaged 800 mg. per cent (range 310 to 2,520); 22 control animals, fed vegetable monkey chow without egg yolk, averaged 340 mg. per cent (range 179 to 513). At autopsy, no distinct lesions of the heart and blood vessels were found in the ground squirrels. Of the 17 yolk-fed prairie dogs, terminal serum cholesterol levels averaged 1,160 mg. per cent (range 270 to 2,670), compared to an average of 180 mg. per cent (range 93 to 354) for 26 control animals; at autopsy easily discernible yellowish plaques were found in the thoracic aorta of 11. Microscopy confirmed moderate atheromatosis and showed considerable aortic medial degeneration (with calcification and cartilage formation) which was positionally unrelated to atheromatous plaques. Hypercholesteremia may have been only a secondary factor in medial lesions since some were found in control animals. Incidental findings in 2 yolk-fed prairie dogs were an aneurysm of the sinus of Valsalva, and an organized mural thrombus in the right atrium. It should be enlightening to explore further the striking difference between the effects of hypercholesteremia upon vascular tissue of these species.

Serum Lipid Levels and Blood Pressures of the African Baboon: An Atherosclerotic Susceptible Primate

David H. Baeder, New York, N. Y., and Nicholas T. Werthessen, San Antonio, Texas

The study of atherosclerosis has been complicated by the fact that its experimental production in animals requires a number of unphysiologic procedures. The lesion which results from these procedures is still the subject of controversy among pathologists as to whether or not this resembles or even has the same etiology as the lesion that is found in man. Recently the group at Louisiana State University and the Southwest Foundation for Research and Education reported on the spontaneous development of an arterial lesion in the baboon which closely resembles that found in man. The lipid studies in their report showed extremely low levels of blood cholesterol.

Because of the importance of these findings, it was felt that a survey was indicated to study the blood lipids and blood pressure of these animals. Blood samples were obtained from a group of African baboons and from a second group inbred in this country for a number of years. Over 1,000 separate lipid determinations showed that the average cholesterol level was 114 mg. per cent. The average lipid P level was 6.5 mg. per cent. The average total lipid value was 565 mg. per cent. The lipoproteins as demonstrated by paper electrophoresis were found predominantly in the beta fraction. Arterial blood pressure averaged 125 mm. systolic and 85 mm. diastolic. Statistical analysis showed a relationship to age, sex, diet and the incidence of the arterial lesion.

Bile Acids and the Time Pattern of Fecal Steroid-C^{14} Excretion, Following Single Injections of Mevalonic Acid-2-C^{14} (P)

William T. Beher, Margaret E. Beher, Gizella D. Baker, and William L. Anthony, Detroit, Mich.

Mice maintained on a basal diet, or a diet supplemented with bile acids, received mevalonic acid-2-C^{14} intraperitoneally. At 24-hour intervals, feces were collected and C^{14} determined in the α and β sterol and bile-acid fractions. In controls, excreted bile-acid-C^{14} assayed 3 times sterol-C^{14} during the first 24 hours. This ratio was reversed throughout the following 72 hours, after which the excreted activities equalized. Cholic acid or its conjugates depressed bile-acid-C^{14} excretion, but failed to alter the time pattern of fecal sterol-C^{14} elimination. Hyodeoxycholic acid greatly increased sterol-C^{14} excretion (shown to be of hepatic origin), had little effect on bile-acid-C^{14} excretion, and increased the total steroid-C^{14} eliminated. Lithocholic acid had a similar though smaller effect. After sacrifice, the livers of cholic acid-treated mice had twice as high β-sterol-C^{14} as livers of controls, while livers of lithocholic and hyodeoxycholic acid-treated animals showed reduced β-sterol-C^{14} levels. Carcass β-sterol-C^{14} levels were unaffected by any of the bile acids. The total amount of sterol-C^{14} synthesized from injected mevalonic acid was similar in all cases. It was concluded that: (a) cholic acid and its conjugates depress bile-acid synthesis in intact mice with normal cholesterol levels; (b) mevalonic acid-2-C^{14} is useful in studying rates and patterns of fecal steroid elimination and bile acid synthesis, but is less satisfactory for cholesterol synthesis studies; and (c) liver cholesterol metabolism is independent of carcass cholesterol metabolism when studied at short intervals under the conditions of this experiment.

Effects of Thyroid Analogues on the Serum Triglycerides and Radioactive Fat Tolerance

Donald Berkowitz, John J. Spitzer, Millard N. Croll, and Bernard Shapiro, Philadelphia, Pa.

The hypocholesterolemic effects of various thyroid analogues have been established previously. The present study was an attempt to determine their effects on other parameters of lipid metabolism, notably the triglycerides and radioactive fat tolerance.

Three groups of 25 patients each with elevated cholesterol levels were treated for prolonged periods of time (3 to 9 months) with triiodothyropropionic acid, detrothyronine, or sodium dextrothyroxin. Half of the subjects had positive evidences of coronary artery disease as manifested by a history of a previous myocardial infarction. The serum cholesterol and triglycerides were measured at monthly intervals. A radioactive triolein tolerance test was done initially and then again after at least 3 months' treatment.

Each of the agents produced a significant lowering of the cholesterol level in 60 to 70 per cent of those treated. The triglycerides were also reduced in over 70 per cent, and the fat tolerance was improved in over half, the degree of improvement being proportional to the reduction in the triglyceride level. The most pronounced cholesterol decreases occurred in patients with initially elevated neutral fat levels. Minimal hypermetabolic side effects were noted in some cases.

Triiodothyropropionic acid, detrothyronine, and sodium dextrothyroxin appear to be effective in lowering the serum cholesterol and triglyceride levels as well as improving fat tolerance.

Comparison of Oral and Intravenous Fat-Tolerance Tests in Patients with Coronary Artery Disease (P)

Donald Berkowitz, David M. Sklaroff, and Millard W. Croll, Philadelphia, Pa.

Previous studies in patients with coronary artery disease have shown that following fat feeding the serum lipemia is increased and prolonged as compared with normal subjects. Although the specific factors contributing to these abnormal tolerance curves are not clear, it is generally accepted that they concern both absorptive as well as clearing mechanisms. The availability of suitable emulsions, both radioactive and nonradioactive, for intravenous use has made it possible to compare the results with these newer agents in the same individuals.

Fifty patients with proved coronary atherosclerosis and impaired oral radioactive fat tolerance were studied following the intravenous administration of a small quantity of an I^{131}-triolein emulsion, and the disappearance rate of the injected fat compared with a group of controls. An additional 10 patients who had sustained a previous myocardial infarction were studied with both an oral and intravenous tolerance test using 600 ml. of a nonradioactive fat emulsion (Lipomul).

In the group treated with the intravenous isotopic fat, the clearance rates were variable and were related to the height of the initial triglyceride level. The overall tolerance curves were considered to be significantly different from the normals in only 25 per cent of the cases.

In the group of 10 who received the nonradioactive fat, 8 subjects demonstrated an impaired oral tolerance. In 3 of these the intravenous response was also abnormal, whereas the other 5 showed normal clearing.

The data presented suggest that an increase in the rate of fat absorption may play a role in the pathogenesis of the hyperlipemic response present in patients with coronary artery disease.

Chemical and Histologic Study of Advanced Coronary Atheromas

David H. Blankenhorn and Larry E. Bolick, Los Angeles, Calif.

Much remains unknown concerning the manner in which calcium accumulates in advanced atheromas. It has been difficult to study the deposition of calcium in these lesions because the majority must be decalcified before they can be properly sectioned. This presentation will describe a micromethod for decalcification of individual atheromatous plaques in a manner permitting determination of total calcium content and calcium removal rate. Calcium is extracted with ammonium ethylenediaminetetraacetic acid and specimens are left intact for histologic examination.

Combined histologic and chemical examination of human coronary arteries reveals that 2 sorts of calcific deposits occur in advanced atheromas. One form, which is rapidly extractable, appears to be calcified in a more diffuse manner than the other, which is slowly extractable. Removal of calcium from the slowly extractable form characteristically leaves discrete lacunar spaces. These spaces seem analogous to the cholesterol clefts formed when lipid-rich atheromas are extracted with fat solvents.

New Method for the Determination of Dihydrocholesterol (3β Cholestanol) In Tissues

Jaime Blum, Eugene R. Arroyo, Vertistine B. Mbaya, and Erwin H. Mosbach, New York, N. Y.

Studies of the metabolism of dihydrocholesterol in mammalian tissues required a method for the

determination of this sterol in the presence of large amounts of cholesterol. The removal of cholesterol by the dibromination method of Schoenheimer was found to be unsatisfactory when the dihydrocholesterol content of the sterol mixture was less than 3 per cent (which is usually the case in normal tissues). The proposed method is based upon the finding that peroxidation of cholesterol-dihydrocholesterol mixtures with performic acid converts cholesterol to cholestane-3β,5α,6β-triol in better than 99.9 per cent yield, leaving the saturated sterol dihydrocholesterol unchanged. The oxidation mixture is resolved into its components by chromatography on silicic acid columns. Dihydrocholesterol in the effluent is determined as the digitonide, either gravimetrically or colorimetrically by the anthrone method. Analyses of known sterol mixtures indicated that 0.5 mg. of dihydrocholesterol was recovered quantitatively from samples containing as much as 99 per cent cholesterol. Application of this method to the analysis of nonsaponifiable fractions of tissues showed that previous estimates of the dihydrocholesterol content of tissues (particularly of atherosclerotic aortas and of gallstones) tended to be too high.

Effect of Triparanol and of D 3:5:3′ Triiodothyronine on Serum Lipid Levels and on the Incidence of Infarction in Dietary-induced Myocardial Infarction in Rats

David F. Brown, Albany, N. Y.

A 40 per cent butter diet supplemented with cholesterol, cholic acid, and thiouracil is known to produce myocardial infarcts in rats. The plasma lipid changes produced by this diet were measured at intervals for 24 weeks in a group of 10 rats (group A). Because it is extremely difficult to assess the therapeutic value of lipid-lowering agents in man, it was decided to note whether their use in these animals could prevent lipemia and simultaneously protect the animals from infarction. In a second group of 10 rats (group B) therefore, triparanol was added to the above diet and in a third group of 10 (group C) D-triiodothyronine was added. Normal plasma lipid levels in these animals were: cholesterol 98 mg. per cent, phospholipid phosphorus 2.6 mg. per cent, and triglyceride 1.4 mEq./L. After 5 weeks on the above regimen, the mean cholesterol levels rose to 1,583 mg. per cent in group A; to 2,016 mg. per cent in group B; and to 443 mg. per cent in group C. Corresponding values for phospholipid phosphorus were 20.5 mg. per cent, 24.1 mg. per cent, and 8.2 mg. per cent, and for triglyceride 17.1 mEq./L., 12.8 mEq./L., and 6.3 mEq./L. After 24 weeks, although little further lipid changes occurred in groups A and C, a progressive increase occurred in group B, the survivors in this group having a mean cholesterol level of 3,525 mg. per cent, phospholipid phosphorus 58.9 mg. per cent, and triglyceride 21.9 mEq./L. Three myocardial infarcts and 1 renal infarct were present in group A, 3 myocardial infarcts in group B, and none in group C.

It was concluded that the occurrence of myocardial infarction in rats ingesting a high-fat diet was related to the magnitude of lipemia the diet was allowed to produce.

Critical Balance Between Saturated and Unsaturated Dietary Fat Necessary to Reduce Serum Cholesterol Levels (P)

Helen B. Brown and Irvine H. Page, Cleveland, Ohio

Our purpose was to determine the amount of polyunsaturated oils which must be substituted for saturated fat in the usual American diet to reduce serum cholesterol levels significantly ($>$ 10 per cent). A series of controlled diet tests lasting 18 days involved normal men (33) and women (13) aged 25 to 55 years. Ordinarily available foods were served, varied only in content of saturated and unsaturated fat.

Serum cholesterol levels were reduced 15 per cent or more when unsaturated cottonseed oil provided 30 per cent total calories and the saturated fat—present in meat, dairy products and eggs—provided 8 per cent or less. When saturated fat was increased by only 1 per cent—to 9 per cent of total calories—serum cholesterol reduction was not significant. As regards polyunsaturated and saturated fatty acid composition of the 40 per cent total calories provided in the form of fat, the balance was again a critical one. Unless 15 per cent of total fat consumption was polyunsaturated fatty acid—1½ times the saturated fatty acid content (P/S = 1.5)—serum cholesterol was not reduced significantly.

The diet was practical, varied and palatable. It provided 2 servings of properly selected and prepared meat a day, in addition to several eggs and an ounce or so of cheese during the week, while still keeping within the necessary dietary limits.

Effects on Blood Cholesterol of Triparanol Given Together with a Diet of the Prudent Type

Mario Campagnoli, Arturo L. Lopez Gil, Leon Press, and Manuel Ruda, Buenos Aires, Argentina

According to many investigators, a reduction of blood cholesterol may lessen the risk of atherosclerosis. Triparanol has been found by many

authors to be a useful agent for the reduction of cholesterol.

Forty consecutive patients with hypercholesterolemia and/or atherosclerosis were given 250 mg. of triparanol daily for up to 3 months, together with a diet composed of: carbohydrates 300 Gm., proteins 70 Gm., fats 80 Gm. (half of them of the unsaturated type), total calories 2,200. A mean reduction of 175 mg./100 cc. was obtained, or 42 per cent. The maximum reduction amounted to 308 mg./100 cc. (from 500 to 192). The minimum reduction was 30 mg./100 cc. These figures, which represent in most cases averages of several determinations, are significant. There were no failures. Contrary to published reports, the withdrawal of the drug did not revert the cholesterol levels to pretreatment figures in patients continuing on the diet. No side effects could be detected. Many patients expressed spontaneously subjective improvement.

Most published reports emphasize that the patients treated with triparanol *were not* on any type of diet, leading one to suspect that at least some of them ate a diet rich in saturated fats and cholesterol, namely, of the atherogenic type. Hence, those results are difficult to evaluate. Our figures, which seem to be better than most obtained on an *ad libitum* diet, lead us to conclude that the effects of triparanol are enhanced by the combined action of a diet of the prudent (Jolliffe) type.

Observations on the Chronic Effects of Triparanol on Cholesterol and Desmosterol Metabolism in Man (P)

Aram V. Chobanian, and William Hollander, Boston, Mass.

The effects of triparanol on cholesterol and desmosterol (24-dehydrocholesterol) metabolism have been studied in 25 patients in doses of 250 mg. daily for 6 to 19 months. Separation and measurement of cholesterol and desmosterol were made by gas-liquid chromatography.

Triparanol produced reductions in serum cholesterol averaging 103 mg. per cent or 36 per cent below control levels. Desmosterol appeared in the serum during the first week of therapy and remained at relatively fixed levels averaging 49 mg. per cent or 17 per cent of the total serum sterols. The mean reduction in total serum sterols averaged 54 mg. per cent or 19 per cent below control levels.

In 5 patients, triparanol produced a mean reduction in conversion of C^{14}-acetate to C^{14}-cholesterol of 53 per cent and a mean reduction in conversion of C^{14}-acetate to total C^{14}-sterols of 35 per cent. The cholesterol "miscible pool" when corrected for desmosterol was reduced by an average of 52 per cent below control levels in 3 patients treated with triparanol, and total sterol pool was reduced by 33 per cent.

Desmosterol concentration of liver tissue in a patient treated 6 months with triparanol was 13 per cent of total sterols as compared to serum desmosterol concentration of 25 per cent. A xanthelasma from a patient treated for 8 months with triparanol had a desmosterol concentration of 10 per cent of total sterols as compared to 18 per cent in the serum.

In conclusion, triparanol produces significant reductions in total serum sterols and in the body sterol "miscible pool." The tissue distribution of desmosterol appears to differ from that of cholesterol.

Iodine Number of Depot Fat and the Degree of Coronary Atherosclerosis (P)

Francis Chucker, Arnold L. Brown, Jr., Bernard F. McKenzie, Ray W. Gifford, Jr., and John L. Juergens, Rochester, Minn.

The purpose of this study was to determine whether a correlation exists between the saturation of depot fat as measured by the iodine number and the degree of coronary atherosclerosis found at necropsy. Seventy-five cases were studied. In each of the first 20, a sample of fat was taken from 5 different sites: the anterior abdominal wall, omentum, mesentery, epicardium and perirenal area. The iodine numbers of fat from the 5 locations did not vary significantly in the individual case, so that in the remaining 55 cases determinations were made only on perirenal fat. The degree of coronary atherosclerosis was estimated by gross observation of the lumen sectioned in multiple areas.

In 19 of 50 nondiabetic normotensive cases, there was little or no coronary atherosclerosis and the iodine number was 65.7 ± 4.6 (S.D.); in 19, a moderate degree of coronary atherosclerosis was present and the iodine number was 68.4 ± 4.0; and in 12, severe coronary atherosclerosis was present and the iodine number was 68.0 ± 3.7. In 16 cases of hypertension, the iodine number was 67.0 ± 4.8, and in all but 3 of these there was significant coronary disease. In 4 cases of diabetes mellitus and severe coronary involvement, the iodine number was 71.6 ± 6.5. In 5 cases of diabetes mellitus and hypertension, the iodine number was 67.3 ± 4.2. There were no significant differences in the iodine numbers among patients of various age groups. There appeared to be no correlation between the saturation of depot fat as measured by the iodine number and the degree of coronary atherosclerosis.

Atherosclerosis in the White Carneau Pigeon Aged One to Twelve Weeks

Thomas B. Clarkson, Robert W. Prichard, and Alvin F. Moreland, Winston-Salem, N. C.

At about 7 months of age, approximately 18 per cent of White Carneau pigeons have grossly visible atherosclerotic lesions, increasing to 60 per cent at 12 months, 90 per cent at 24 months and 100 per cent at 36 months. This study describes the *microscopic* lesions of atherosclerosis in the White Carneau pigeon at weekly intervals from weeks 1 to 12 after hatching.

At 1 week 20 per cent of squabs (2 of 10) have focal intimal thickening by endothelial and fibrocytic cells, without significant lipid deposition. By the third week 58 per cent of squabs (7 of 12) are affected. The group at the end of 5 weeks showed 67 per cent with the disease (8 of 12). These 5-week birds have both free and intracellular lipid with an overlying fibrocytic cap. At 10 weeks an incidence of 100 per cent is reached (8 birds).

Young pigeons are fed by the parents during the first 4 to 6 weeks of life. Initial feedings are with "pigeon milk," desquamated crop-lining cells principally, providing 59 per cent protein and 33 per cent fat. Beginning with the third to fourth day, small grains become mixed with the "milk," until at 7 to 14 days their entire food is grain (or artificially prepared pellets), as in the adult. In this study the admixture was that of pigeon "milk" and Purina Pigeon Pellets.

Further Localization of Lipoprotein Lipid Anomalies in Coronary Arterial Disease (P)

Louis Cohen, Ljubica Dobrilovic, and Richard J. Jones, Chicago, Ill.

The more precise localization of the lipid abnormalities in coronary arterial disease is suggested from the study of lipids in serum lipoproteins of density < 1.019, 1.019 to 1.063 and > 1.063, in 45 healthy controls and 30 patients with coronary disease, and 16 closely matched subjects from each group.

In the larger study, the patient group had significantly greater amounts of cholesterol and phospholipid in the 2 fractions of lower density, which accounted completely for the plethora of these lipids in whole serum. In the matched groups, however, the mean values of the cholesterol, phospholipid and cholesterol/phospholipid ratio in both whole serum and lipoproteins of density 1.019 to 1.063 were closely comparable.

Despite these similarities, the matched groups differed. In the matched patient group, the cholesterol and phospholipid in lipoproteins of density < 1.019 were significantly ***higher***: cholesterol 39.4 vs. 28.9 mg./100 ml. ($t = 2.87$), phospholipids 36.9 vs. 26.6 ($t = 2.51$); and these lipids in lipoproteins of density > 1.063 were significantly *lower:* cholesterol 51.7 vs. 64.1 mg./100 ml. ($t = 2.63$), phospholipids 109 vs. 124 ($t = 2.23$). The cholesterol/phospholipid ratios in corresponding fractions were comparable in the matched groups.

These observations indicate that even when whole serum lipids are comparable to those found in health, patients with coronary disease suffer a plethora of cholesterol and phospholipid in lipoproteins of density < 1.019. This, and the paucity of lipids in lipoproteins of density > 1.063, suggest that the lipids in these 2 fractions may be in some sort of imbalance in coronary disease.

Clinical and Serum Lipid Effects of a Combination of Norethynodrel plus Ethynylestradiol 3-Methyl Ether in Postmenopausal Women

William D. Cohen, Roger W. Robinson, and Norio Higano, Worcester, Mass.

Previous studies have shown that, although estrogen administration at adequate dosages to postmenopausal women resulted in favorable serum lipid effects, there was a significant incidence of undesirable vaginal bleeding. In the present study an attempt was made not only to avoid this complication but also to observe any serum lipid effects by continuous treatment of 21 women with intact uteri with varying dosages of norethynodrel plus 1.5 per cent ethynylestradiol 3-methyl ether, a mixture having both estrogenic and progestational activities. An additional 16 previously hysterectomized women were also included. In general, this drug was well-tolerated, with increased sense of well-being, relief of menopausal symptoms, and improved skin texture. Nineteen per cent (7/37) had undesirable nausea and occasional vomiting. Other common side effects included transitory breast tenderness and leg-muscle cramps. In a few instances, persistent breast hypertrophy, migraine, and increased vaginal secretions were noted. In order to avoid break-through bleeding, increasing doses were required in most of the patients. Twenty mg. daily maintained an intact endometrium in some patients, 25 or 30 mg. were required by a few, and 40 mg. daily by 1. In this way uterine bleeding has been suppressed for as long as 2½ years in several patients. Typical estrogenic effects on the serum lipids were seen at all dosage levels from 5 to 40 mg. daily. Vaginal Papanicolaou smears showed a uniform estrogenic effect on the mucosa, and no malignant cells have been observed.

Differential Effects of Dietary Cholesterol and Fat upon Human Serum Lipid Levels and Fecal Sterols (P)

William E. Connor, Daniel B. Stone, and Robert E. Hodges, Iowa City, Iowa

Recent evidence has suggested that dietary cholesterol greatly influences human serum cholesterol levels. This study was designed to examine interrelationships between dietary cholesterol and fat intakes of varying compositions.

Three normal and 3 diabetic men were hospitalized and fed in sequence 4 different diets of mixed, natural foods. Each diet, eaten for 4 weeks, provided in terms of total calories 16 per cent protein and 40 per cent fat, composed only of long-chain fatty acids.

The diets of periods I and II were identical in fatty-acid composition: saturated 39, oleic 53, and polyunsaturated 8 per cent; iodine value 61. Period I contained 725 mg. of cholesterol daily. Period II was cholesterol-free. Fatty-acid composition in periods III and IV was: saturated 18, oleic 53, and polyunsaturated 29 per cent; iodine value 98. Period III was cholesterol-free. Period IV contained 725 mg. cholesterol.

The mean serum cholesterol decreased 42 mg. per cent ($P < 0.001$) with the removal of cholesterol from the diet (period I to II). Increasing the iodine value of the cholesterol-free diet (period III) did not alter mean serum cholesterol concentrations. Adding cholesterol (period IV) increased mean serum cholesterol 18 mg. ($P < 0.01$). Normal and diabetic subjects responded similarly. Serum phospholipid changes paralleled cholesterol changes throughout. Fecal sterol excretion decreased from periods I to II and increased sequentially in periods III and IV.

In this study dietary cholesterol influenced serum lipid levels. This effect seemed greater when dietary fat was more saturated and less when it was more polyunsaturated.

Influence of Age upon Sterol Synthesis in the Normal Artery (P)

Seymour Dayton and Sam Hashimoto, Los Angeles, Calif.

In vitro synthesis of cholesterol and its precursors from labeled acetate, by aortas of normal cockerels of different ages, displayed a decrease with increasing body weight over the range 350 to 1,500 Gm. This was particularly pronounced, and approximately linear, in the relationship between log aortic weight and log total digitonin-precipitable radioactivity per Gm. of aortic tissue ($r = 0.97$). The weight-related differences were not due to alterations in permeability of the tissue nor in activation of the substrate, since conversion of acetate carbon to CO_2 did not show a similar relationship. Thoracic and abdominal aorta displayed comparable synthesis rates. After a 3-hour incubation, 75 per cent of the digitonin-precipitable radioactivity was present as "high-counting companions" of cholesterol, removable by bromination.

Mevalonate was more efficient than acetate as a precursor of digitonin-precipitable sterol, but 94 per cent of the radioactivity was removed by bromination. With mevalonate as with acetate, total sterol synthesis was inversely related to aortic weight ($r = 0.92$ for the log-log relationship). Conversion of substrate to CO_2 was unrelated to body weight, and was smaller in the case of mevalonate (0.05 per cent) than with acetate (2.4 per cent).

These findings suggest the possibility that sterol synthesis in the normal artery wall may be chiefly a manifestation of tissue growth.

Preliminary results in the rat suggest a similar inverse relationship between age and aortic cholesterol synthesis.

Changing the type of dietary fat (30 per cent safflower oil vs. 30 per cent coconut oil) appeared to be without effect upon the in vitro incorporation of acetate into cholesterol and its precursors by the rat aorta.

Effect of Reticuloendothelial Stimulating Agents on Hepatic and Plasma Lipids (P)

Nicholas R. Di Luzio and Stephen J. Riggi, Memphis, Tenn.

Previous studies have demonstrated that the intravenous injection of Zymosan, a cell-wall preparation of *Saccharomyces cerevisiae,* produces a marked proliferation of reticuloendothelial (RE) cells and an increase in their functional activity. The induction of RE hyperactivity in rats maintained on atherogenic diets for 14 days was associated with a significant decrease in liver and plasma cholesterol concentrations. An active fraction of Zymosan in stimulating phagocytosis and inducing RE hyperplasia has been identified as the polysaccharide, glucan. In an attempt to evaluate the relationship between the functional state of the RES and the inhibition of hepatic cholesterosis, the influence of various RE stimulatory and nonstimulatory fractions, isolated from Zymosan, on liver and plasma cholesterol and triglyceride concentrations of rats maintained on high-cholesterol diets was determined. In the glucan series, additional rats received a cholesterol suspension by oral intubation for 4 days.

The fractions isolated from Zymosan which were active in stimulating the RES were found to produce a significant inhibition in the accumu-

lation of liver ester cholesterol and triglyceride. Conversely, the nonstimulatory fraction was ineffective. Glucan produced a marked reduction in the accumulation of liver ester cholesterol which was inversely related to the extent of induced cholesterosis. Although the mechanism by which RE stimulation inhibits the accumulation of cholesterol is not as yet defined, these findings contribute to the elucidation of a relationship between the functional activity of the RES and the metabolism of exogenous cholesterol.

Degenerative Disease and Carbohydrate Intolerance

Harold L. Dobson, Houston, Texas

This study was carried out to determine the incidence of carbohydrate intolerance in patients with a variety of degenerative disease diagnosed before age 56. No patient was included if a diagnosis of diabetes mellitus had been made or suspected previously. Included were 14 patients with myocardial infarction, 9 patients with "arteriosclerotic heart disease" without overt evidence of myocardial infarction, and 16 patients with gallstones. In addition, 5 patients with early microaneurysms and no previous history of diabetes, and 12 older patients with gangrene of the foot and no previous history of diabetes were included for comparison.

In the myocardial infarction group, there were 9 males and 5 females. The standard glucose-tolerance test (GTT) was abnormal in 10 and the cortisone glucose-tolerance test (C-GTT) was abnormal in 3 of the remaining 4. The women tended to be obese and had a family history of diabetes. This was not true in the men. There were 3 females and 6 males in the "arteriosclerotic heart disease" group. GTT was abnormal in 6 and the C-GTT was abnormal in the remaining 3. One-half of these patients were obese. In the gallbladder group there were 2 males and 14 females. GTT was abnormal in 6 and the C-GTT was abnormal in 4 of 8 of the remaining patients. Obesity and family history of diabetes were common in this group. Three of the patients with microaneurysms had an abnormal GTT and the remaining 2 had abnormal C-GTT. All patients with gangrene of the foot showed some stigmata of carbohydrate intolerance. This study suggests a significant correlation between early degenerative disease and carbohydrate intolerance.

Blood Flow Patterns in Relation to the Formation of Deposits in Extracorporeal Shunts

Harry G. Downie, Guelph, Ontario, Canada, Edmund A. Murphy, Toronto, Ontario, Canada, Harry C. Rowsell, Guelph, Ontario, Canada, and James F. Mustard, Toronto, Ontario, Canada

A close analogy, both topographical and histochemical, has been demonstrated between early atherosclerosis and the deposits formed in plastic vessel models used as extracorporeal shunts. The formation of encrustations at these characteristic sites is probably in part related to changes in flow.

Cinematography has been used to demonstrate the turbulence and eddy formations which are present at the sites where deposits form on the lateral walls of the models of bifurcations. The area of deposit is restricted to the site of maximum turbulence and eddy formation. The nose of the bifurcation also shows some deposits associated with an altered flow.

In plastic models of unpaired intercostal vessels, the lines of flow can be seen from the patterns of the early platelet deposits. Cinematography has shown that the region of greatest change in flow is at the lateral edges of the orifices. It is at this region that the characteristic butterfly-shaped deposits occur. At the proximal lip which is spared, there is no obvious change in flow. In the main channel the reduced volume of flow and turbulence distal to the orifices is associated with increased thrombus formation. In these models the early butterfly-shaped deposits gradually coalesce, producing a ladder-like appearance which is similar to the pattern of development of atherosclerosis about unpaired intercostal vessels.

These studies, which have also been done with other models, demonstrate that turbulence and eddy formation are important in causing and localizing encrustations and probably the early lesions of atherosclerosis.

Turnover Rate of Kidney Cholesterol (P)

Charles H. Duncan and Maurice M. Best, Louisville, Ky.

Mevalonic acid-2-C^{14} was given intraperitoneally to 15 male rats and 1 week later the specific activity of serum cholesterol and the specific activity and total cholesterol-C^{14} content of each kidney determined. Mean specific activity of serum cholesterol was only 1.8 per cent (S.D. 0.5) that of kidney cholesterol; mean total cholesterol-C^{14} in the right kidney was 102.2 per cent (S.D. 8.5) that in the left kidney. This selective labeling of kidney cholesterol, resulting in a specific activity many times higher than that of serum cholesterol with which it can exchange, and the essentially identical cholesterol-C^{14} content of the 2 kidneys permit determination of turnover rate of kidney cholesterol.

Twenty-one additional rats were similarly given 0.3 to 0.6 μc. mevalonic acid-2-C^{14} and 1 week later the left kidney removed. At intervals of 2, 4 and 6 weeks after nephrectomy, one-third of the

animals were killed and the remaining kidney removed. The mean cholesterol-C^{14} content of the final kidney, expressed as per cent that of the kidney initially removed, was: 2 weeks, 65.7 (S.D. 5.1); 4 weeks, 42.7 (S.D. 2.2); and 6 weeks, 24.7 (S.D. 2.2.). Half-life of kidney cholesterol was thus approximately 22 days.

Rats made hyperthyroid by daily injection of 0.4 μm. L-thyroxin/Kg. body weight starting at the time of nephrectomy had significantly lower residual kidney cholesterol at 4 weeks, 34.1 per cent (S.D. 1.0) that of the initial kidney, giving a half-life of 18 days ($P < 0.001$).

Effect of Blood Pressure on the Entrance of Albumin into the Aortic Wall of the Dog (P)

Leroy E. Duncan, Jr., Katherin P. Buck, and Almorris Lynch, Bethesda, Md.

Labeled albumin and labeled cholesterol enter canine aortic wall with a gradient of rates. They enter fastest proximally and progressively less rapidly down the length of the aorta. Early in the development of experimental canine atherosclerosis, cholesterol accumulation forms a similar gradient. It seems likely that the mechanism leading to the gradient in each case is similar. In an effort to clarify this mechanism, we have studied the effect of blood pressure on the entrance of albumin into aortic wall. Hypertension was produced in dogs by section of the carotid sinus nerves and the vagi. The elevation of pressure produced a striking increase in the entrance rate in the proximal aorta, a moderate increase in the mid-aorta, and no increase in the distal aorta. Thus hypertension made the gradient of rates steeper. Faster entrance of albumin was not due to some dynamic characteristic of pressure associated with the hypertension since it also occurred during elevation of nonpulsatile pressure in aortas studied in vitro. Either the hypertension itself or the associated aortic stretching could have increased the entrance rates. If it was pressure, there was decreased susceptibility to this pressure distally. If it was stretching, there was either decreased susceptibility or decreased stretching distally. The latter is known to occur. Experimental separation of the variables stretching and pressure may exclude some of these possibilities. It appears likely that the mechanism by which hypertension accentuates the gradient is related to the mechanism of the development of the gradient at normal pressure.

Effect of 3 [4-(4-Hydroxyphenoxy)phenyl] propionic Acid (T_0Prop) on In Vitro and In Vivo Cholesterol Biosynthesis

Charles H. Eades, Jr., Morris Plains, N. J.

Our interest in 3,3′,5-triiodothyropropionic acid (T_3Prop) and its effects on cholesterol metabolism prompted us to determine if the iodine-free analogue has any such properties. T_0Prop was prepared by replacing the iodine of 3-iodothyropropionic acid with hydrogen. BMR studies in rats with T_0Prop revealed it did not stimulate oxygen consumption, in contrast to T_3Prop. Inclusion of 2 μM. of T_0Prop in a rat-liver homogenate system containing 2 μc. sodium acetate-1-C^{14} inhibited, in vitro, C^{14} incorporation into nonsaponifiable lipid fraction (which contains cholesterol) 67.5 per cent (control, 13,746 disintegrations per min. per mg. (d.p.m./mg.) cholesterol; T_0Prop, 4,470). To test this inhibition in vivo, normal male adult rats were fed regular chow diets containing 400 mg. per cent T_0Prop. Controls were pair-fed. After 2 weeks on the diet, the rats were injected intraperitoneally with 48.8 μc. sodium acetate-1-C^{14} (2 mg. in 4 ml. saline), and sacrificed 4 hours later. Incorporation of C^{14} into the nonsaponifiable lipid fraction of liver was 52.5 per cent lower in the group fed T_0Prop than in control (3,541 d.p.m./mg. cholesterol compared to 7,450 for control). Serum and aorta analyses revealed comparable results. Cholesterol contents of serum and liver were not significantly different in the 2 groups at the end of the 2-week study. Similar experiments with mice have yielded similar results. Data from these studies indicate that T_0Prop has an inhibitory effect on cholesterol biosynthesis from acetate. Extended treatment time may be required to show gross effects on liver and serum cholesterol content.

An Objective Method for Grading Atherosclerotic Lesions

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An objective method has been developed for evaluating the degree to which arteries are involved with sudanophilic, fibrous, and calcified lesions of atherosclerosis. The arteries are opened longitudinally, fixed flat, and stained with Sudan IV under controlled conditions. A soft x-ray and a black-and-white photographic negative are scanned with a flying spot scanner which generates an electrical (video) signal proportional to transmittance. An electronic analyzing device then measures the total time during which the signal is greater than an adjustable reference level. At different settings of the reference level one thus obtains the area of the specimen involved with fatty streak, focalized fibrous plaque, calcified plaque, and the total area of the specimen. From these values the per cent area involved with each of the 3 types of lesions can be calculated.

An alternative analyzing device also measures the integral of the video signal. With suitably prepared negatives this provides a measure of the degree of sudanophilia ("redness") or a measure which involves the mass per area of the artery in excess of that corresponding to the base or normal region.

Results obtained to date indicate that per cent area involvement can be measured with a reproducibility of 5 to 10 per cent. The measurement of "redness" can be obtained with sufficient reproducibility to permit grouping into approximately 15 grades. A product-moment correlation of 0.95 has been obtained between per cent area calcified and weight of calcium (calcified) per cm. of aorta surface as determined by chemical analysis.

Total Protein in the Serum of Rabbits with Hypercholesteremia Hyperlipemia

Arecell F. Engel and O. J. Pollak, Dover, Dela.

Hypercholesteremia was induced in 32 of 44 white New Zealand buck rabbits by feeding eggs fried in wheat-germ oil, oat oil, oil of sesame or Crisco. Cholesterol values of 31, 770 and 1,141 mg. per 100 ml. of blood were accompanied by total blood lipid values of 370, 1,250 and 3,500 mg. per 100 ml. and by total protein of 5.21, 7.00 and 7.70 Gm. per 100 ml. of serum. Total lipid increased far more than cholesterol; protein levels rose less.

Average values for serum albumin of these rabbits were 2.84, 3.62 and 3.51, those for globulin, 2.37, 3.38 and 4.19 Gm. per 100 ml., respectively. Thus, hyperglobulinemia was largely responsible for increase in total protein. Alpha-globulin increased but slightly; its values were 0.66, 0.74 and 0.86 Gm. Increase in beta-globulin was marked; it averaged 1.11, 1.38 and 1.87 Gm. per 100 ml., or 16.0, 20.1 and 23.0 per cent of total protein, respectively. Gamma-globulin equaled 1.02, 1.33 and 1.16 Gm. per 100 ml. of serum, the decrease reflecting readjustment of liver parenchyma.

The frequency of free amino acids in serum of rabbits on the diets increased. However, there was no parallelism between amino-acid appearance and the rise of total protein, various protein fractions, total lipid, or cholesterol. The frequency of certain amino acids increased regularly, namely, that of cysteine, histidine, lysine, norleucine, serine, threonine and tyrosine. Alanine and methionine frequency decreased. The same amino-acid shifts were recorded in extracts of aortas of rabbits with induced hypercholesteremia-lipemia. The single exception of parallelism in these shifts was the behavior of alanine, which disappeared from the serum but increased in the aortas of the treated rabbits.

Lipid Metabolic Studies in Patients with Essential Hypertriglyceridemia (P)

Hyman Engelberg, Beverly Hills, Calif.

Various lipid metabolic studies were performed in 16 patients who had a marked increase in serum triglycerides, and who had no evidence of diabetes, nephrosis, hypothyroidism, or liver disease. In addition to lipid measurements, the following determinations were made in most of these subjects: plasma heparin levels, the lipolytic response to injected heparin, the presence of plasma inhibitors of post-heparin clearing factor lipase activity, the removal rate of ingested fat (fat-tolerance tests), serum free-fatty-acid and glycerol levels, and studies of endogenous plasma clearing factor activity.

In these individuals with a severe disturbance of triglyceride metabolism, plasma heparin levels were normal. In the majority, the response to injected heparin was normal. However, in 1 young girl there was no demonstrable clearing factor, in vitro or in vivo, after heparin, and in 1 other subject this response was much decreased. An inhibitor of lipolysis was found in only 1 patient. Fat-tolerance studies gave variable results. However, a normal removal rate of ingested fat was found in some of these subjects. Serum free-fatty-acid and glycerol levels were not abnormal. Peculiarly, endogenous plasma clearing factor activity was persistently present in several of these individuals with marked lipemia.

These findings indicate that this syndrome is of diverse etiology, and that one of its causes is a defect, of one type or another, in the heparin lipoprotein lipase enzymatic mechanism. It is suggested that excessive triglyceride synthesis by the liver is an etiologic factor in other cases.

Effect of Sulfated Mucopolysaccharides and of Endogenous Plasma Heparin(s) on Thromboplastin Generation

Hyman Engelberg, Beverly Hills, Calif.

The thromboplastin generation test of Biggs and McFarlane evaluates factors involved in the first stage of clotting, the formation of thromboplastin. This process is inhibited by very small quantities of heparin. It was desirable therefore to evaluate the effect of extracts of endogenous plasma heparin(s) upon thromboplastin generation since some investigators still question the normal presence of heparin in the blood. In addition, the action of heparin monosulfate, B-heparin (chondroitin sulfate-B), and chondroitin sulfate-A upon thromboplastin generation was studied, as these sulfated mucopolysaccharides may also be present in the

final product obtained by our heparin extraction procedure.

Heparin monosulfate had approximately one-tenth the inhibitory activity of heparin, B-heparin was less active than heparin monosulfate, and chondroitin sulfate-A was almost inactive. The endogenous plasma heparin(s) extract had an inhibitory effect upon thromboplastin generation which was comparable to that of commercial heparin. These results afford further evidence that heparin is present in plasma, that it is extracted by our method, and that biologic activity can be demonstrated in the final product.

Studies of Human Serum and Plasma Inhibition of Post-Heparin Clearing Factor Lipase Activity

Hyman Engelberg, Beverly Hills, Calif.

Serum inhibition of post-heparin clearing factor lipase activity was evaluated in 82 subjects. Inhibition of clearing occurred in 63 instances, whereas inhibition of lipolysis only occurred with 27 of the 82 sera. Lipolysis was increased by added serum in 32 experiments. Thus there was little correlation between inhibition of clearing and inhibition of lipolysis, the latter occurring less often and in a smaller degree. In 17 patients, inhibition by serum and plasma aliquots was studied. Plasma contains less inhibitory activity than serum, and facilitates lipolysis as frequently as it inhibits it.

There was no correlation between serum inhibitors and levels of cholesterol or low-density lipoproteins in 63 individuals. These results indicate that normally inhibitors of clearing factor lipase (lipoprotein lipase) activity are not an important factor regulating serum lipid levels in man.

Coronary Heart Disease in a Total, Natural Community—Tecumseh, Michigan (P)

Frederick H. Epstein, Ralph L. Brandt, Norman S. Hayner, Benjamin C. Johnson, John A. Napier, Millicent W. Payne, and Thomas Francis, Jr., Ann Arbor, Mich.

During the first phase of a prospective epidemiologic study in Tecumseh, 8,641 persons, representing 90 per cent of the population, were examined. Coronary heart disease (CHD), presenting as myocardial infarction (MI), angina pectoris (AP) or characteristic electrocardiographic abnormalities, singly or in combination, was manifest in 12 men and 7 women between age 20 and 39; in 81 men and 52 women aged 40 to 64; and in 43 men and 39 women aged 65 and over. Corresponding prevalence rates per 1,000 in these 3 age groups, among men and women respectively, were: 11 and 5, 90 and 58, 208 and 148. Below age 40, the diagnosis was based more commonly on "silent" electrocardiographic changes. A history of MI and/or AP was presented by 39 men and 21 women between age 40 and 64, and 22 men and 12 women beyond age 64; "silent" electrocardiographic abnormalities accounted for the remainder. MI, AP and "silent" electrocardiographic changes showed similar associations with serum cholesterol or blood pressure levels. Elevation of 1 or both of these variables occurred in 57 per cent of the men and 70 per cent of the women with CHD; at older ages, these associations were more pronounced in women than men. Familial aggregations of CHD within kindreds and households are being studied. Preliminary comparisons between successive generations showed no apparent reduction in longevity or excessive mortality from cardiovascular disease among the parents of propositi. More detailed analysis of the complete data on families will permit an assessment of interactions between genetic and environmental etiologic factors.

Impairment of Adipokinesis—a Defect in Essential Hyperlipidemia

Elaine B. Feldman, Ramnath V. Nayak, and Anne C. Carter, New York, N. Y.

The adipokinetic effect of human growth hormone (Raben) was studied by measuring levels of serum free fatty acids in fasting subjects before and 4 hours after intramuscular administration of growth hormone, 2 mg. to a child, 4 mg. to adults. Levels of free fatty acids rose 37 per cent (mean of 3 studies, 2,237 μEq./L. to 3,022 μEq./L.) in a 10-year-old dwarfed boy with idiopathic hyperlipemia, 48 per cent (791 μEq./L. to 1,170 μEq./L.) in a 34-year-old man with idiopathic hyperlipemia, and 54 per cent (671 μEq./L. to 1,032 μEq./L.) in a 51-year-old woman with idiopathic hypercholesteremia. Levels of serum cholesterol were unchanged; serum triglyceride levels decreased. After administration of saline, levels of free fatty acids rose 62 per cent (1,460 to 2,373 μEq./L.) in the child, 68 per cent (500 to 843 μEq./L.) in the man, and 45 per cent (654 to 947 μEq./L.) in the woman. Following intravenous injection of 35 mg. of heparin in the child, free fatty acids rose 91 per cent (2,185 to 4,180 μEq./L.) and triglyceride levels fell. In 4 healthy subjects given the same hormone preparation, a mean rise of free fatty acids of 94 per cent (702 to 1,360 μEq./L.) resulted. After saline injection, the mean rise of free fatty acids was 46 per cent (690 to 1,007 μEq./L.). Levels of serum triglycerides and cholesterol were unchanged. The differences observed suggest that in essential hyperlipidemia there is a disturbance of the in vivo adipokinetic effect of growth hormone.

Is There a "Chylomicron Lipase" as well as a Lipoprotein Lipase? (P)

Robert H. Furman, and Charles W. Robinson, Jr., Oklahoma City, Okla.

Recent studies from the authors' laboratory have demonstrated in vitro lipoprotein lipase activity in post-heparin plasma from certain hyperlipemic subjects (heparin-unresponsive hyperglyceridemia) who show little or no in vivo free fatty acid (FFA) release or "clearing" after heparin injection. FFA release is marked when post-heparin plasma from such patients is subjected to in vitro sonic oscillation (sonation) and then incubated at 37 C. Normal lipoprotein lipase, in the form of post-heparin plasma from healthy volunteers, when added to hyperglyceridemic plasma from these heparin-unresponsive subjects and incubated, causes FFA release. Thus the chylomicrons in this disorder may be presumed "normal" since they are adequate substrate for lipase present in post-heparin normal plasma. Sonation has been shown to increase the concentration of lipid-protein moieties of density greater than chylomicrons at the expense of chylomicron lipid. Thus sonation produces lipid-protein moieties, the glyceride of which is adequate substrate for lipoprotein lipase.

The distinguishing clinical and laboratory features of "heparin-unresponsive hyperlipemia" and the studies mentioned above prompt us to suggest that normally 2 lipases are present following heparin injection. One may be regarded as catalyzing the lipolysis of chylomicron glyceride ("chylomicron lipase"), the other of lipoprotein glyceride ("lipoprotein lipase"). It is suggested that the immediate cause of "heparin-unresponsive hyperlipemia" is deficiency of "chylomicron lipase."

Heparin-induced Thrombocytopenia in Man

Seymour Gollub and Alex W. Ulin, Philadelphia, Pa.

Seven normal human subjects showed acute, reversible thrombocytopenia after administration of intravenous heparin. The phenomenon was repeated within 1 hour after return to normal (1 subject) and within 1 week (1 subject). There was good coincidence between initiation, time of maximal effect and total duration of the thrombocytopenia and the prolongation of the whole-blood clotting times. In general, onset and duration of maximal thrombocytopenia usually lagged behind the Lee-White time. In the 1 subject tested, neutralization of the heparin with protamine resulted in prompt return to normal level of the Lee-White time, and a more rapid return to normal of platelet count. Here also, platelet return lagged behind the Lee-White return. The acute thrombocytopenia could be reversed by neutralization of heparin and also could be immediately reinduced a second time. The data suggest that transient sequestration, rather than destruction and replacement of platelets, is the mechanism of the effect.

Histoenzymatic and Histochemical Study of Human and Experimental Atherogenesis, Part II (P)

I. Ernest Gonzalez, Birmingham, Ala.

Human aortas, coronary arteries, cerebral, carotid and iliac arteries have been studied by histochemical methods. The accumulation of neutral fats, cholesterol, cholesterol esters, lipoproteins and lipofuscins within atherosclerotic lesions in human arteries may be closely associated with the phagocytic activity of intimal cells. Histoenzymatic studies suggest that beta-lipoproteins and other plasma lipids may be phagocytized by macrophages located adjacent to the endothelium and possibly by the endothelial cells of arteries. Once the lipid is within the "foam cell" located in the intima, it is readily hydrolyzed by esterases and lipases capable of hydrolyzing esters of myristic, stearic, and oleic acids. The oxidation of fatty acids by beta-hydroxy-butyric-dehydrogenase is not demonstrable within the atherosclerotic lesion. The "foam cell" within the intima contains high concentrations of aminopeptidase which hydrolyzes a variety of peptides and possibly lipoproteins. When the "foam cell" laden with lipid degenerates within the intima, the lipid is spilled into the extracellular space and forms the nidus of the early atheromatous lesion.

These studies suggest that the process of atherogenesis may not totally depend on passive filtration and imbibition of plasma lipid into the intimal space. The demonstration of high concentrations of esterases, lipases and aminopeptidases within the intima suggests an in situ metabolism of lipid complexes, a phenomenon which may be of profound importance in atherogenesis. Enzyme systems within the intimal cell may play an important role in the evolution of the atheromatous lesion by altering beta-lipoproteins, cholesterol esters, cholesterol, neutral fats and producing insoluble residues which accumulate in the intima.

Interrelations of Thrombosis, Coronary Arteriosclerosis and Myocardial Infarction in Diabetes Mellitus (P)

Fairfield Goodale, Assaad Daoud, Kyu T. Lee, and Rudolfo Florentin, Albany, N. Y.

It is well established that myocardial infarction is more common in diabetic than nondiabetic North Americans. Since myocardial infarcts are usually the result of thromboses developing in arteriosclerotic coronary arteries, differences in number of infarcts between 2 groups are most likely the result of either differences in blood-clotting characteristics (hematologic factor) or in amount of coronary arteriosclerosis (local factor), or both. Surprisingly little objective information is available on the role of either factor.

To study the hematologic factor, we first compared the number of thromboemboli in the venous and pulmonary circulations of 143 autopsied diabetics (all white) with 143 nondiabetic controls. Second, by thromboelastograph we compared the clot-lysis times of 60 living diabetics with 60 nondiabetic controls. The diabetic and nondiabetic patients showed no significant differences between them in either the number of thromboemboli or in clot-lysis times.

To study the local (arteriosclerosis) factor, we made objective measurements of the amount of coronary arteriosclerosis in 60 autopsied diabetics and 60 nondiabetic controls. We also compared the number of coronary occlusions and myocardial infarcts. The diabetics had more arteriosclerosis, and twice as many coronary occlusions and myocardial infarcts as the controls. However, when the same diabetic group was rematched, not only for age and sex, but with a nondiabetic group having the same amount of coronary arteriosclerosis, the differences in number of coronary occlusions and myocardial infarcts almost disappeared.

These data suggest that in diabetics the high incidence of myocardial infarction is more closely related, not to a clotting or clot-lytic abnormality, but to an increased amount of coronary arteriosclerosis.

Chain Length of the Saturated Fatty Acids and the Effect of Dietary Triglycerides on Serum Cholesterol Concentration in the Dog (P)

Francisco Grande, Minneapolis, Minn.

After a period on a low-fat diet (LFD) with 4 per cent of fat calories, 2 groups of dogs were fed alternately, for periods of 2 weeks each, 2 diets containing a fat supplement (40 per cent of the total calories) added to LFD. The supplements were coconut oil (CNO) and an artificial triglyceride containing mainly saturated fatty acids of 8 and 10 carbon atoms (MCT). Mean serum cholesterol of 7 dogs was 183 mg./100 ml. (SE ± 17.5) on LFD, 310 mg. (SE ± 45.0) on CNO, and 230 mg. (SE ± 27.3) on MCT. The cholesterol difference (CNO minus MCT) was 80 mg. (SE ± 25.0, $P < 0.018$). Average food intake was 59 cal./Kg./day for the CNO periods and 34 cal./Kg./day for the MCT periods.

The experiment was repeated with the supplements given by stomach tube. Olive oil and safflower oil were added to MCT to match the monoene and polyene content of CNO. Mean serum cholesterol of 12 dogs was 181 mg./100 ml. (SE ± 13.9) on LFD, 319 mg. (SE ± 22.9) on CNO, and 203 mg. (SE ± 14.6) on MCT. The cholesterol difference (CNO minus MCT) was 116 mg. (SE ± 15.1, $P < 0.0001$). Average food intake was 77 cal./Kg./day for the CNO periods and 70 cal./Kg./day for the MCT periods. Sixty per cent of the cholesterol increase was in the alpha-lipoprotein and 40 per cent in the beta. Lipid phosphorus changed parallel to cholesterol. It is concluded that glycerides of saturated fatty acids with 12 or more carbon atoms produce cholesterol levels significantly higher than do glycerides of saturated fatty acids with 8 and 10 carbon atoms.

Production of Vascular Lesions by Bacterial Endotoxin

Mary E. Gray, Virgil S. LeQuire, John L. Shapiro, and Joseph M. Merrill, Nashville, Tenn.

Vascular lesions have been produced in 150 rabbits by single intravenous injections of a bacterial endotoxin, Shears' polysaccharide. Dosage ranged from 5 to 400 μg./Kg. Time of autopsy varied from 5 minutes to 10 days after injection.

An abnormal degree of endothelial vacuolation appeared within 5 minutes after injection in arteries of all sizes. This decreased in prominence after 18 hours. There was a degenerative arteritis involving the small muscular arteries and arterioles. This was characterized by endothelial vacuolation, palisading and sloughing, intimal thickening, changes in the internal elastic membrane, medial vacuolation, hyaline changes and pyknosis of the nuclei of smooth muscle cells. Occasional thrombi were found, occurring more frequently at doses above 20 μg./Kg. Eight to 12 hours after injection, localized accumulations of lipid droplets were found in the walls of some of the small muscular arteries. These droplets disappeared within 18 to 24 hours after injection. The pulmonary vascular bed was the principal site of involvement with all dosages of endotoxin. In addition, with the larger dosages other vascular beds were affected.

Small but abnormal amounts of embolic fat were found in the pulmonary vessels of the majority of animals.

The effect of cholesterol feeding on the vascular response to endotoxin is being studied.

Influence of Heparin on the Electrophoretic Mobility of Lipoproteins

Marshall E. Groover, Jr., Washington, D. C.

Concentrated heparin (400 mg./ml.) injected into the fat layer of the anterior abdominal wall will increase the electrical activity of that individual's lipoproteins as measured by filter-paper electrophoresis. When the point of application is identified and the stained strip analyzed with a recording densitometer on cross-section paper, the distance from the point of application to the center of the beta-lipoprotein curve may be read in millimeters or expressed in per cent of the distance migrated by the albumin peak of the same strip.

Six individuals were selected because of a history of myocardial infarction and a positive assay for lipid mobilizer factor. These were paired with individuals of comparable age, weight, height and 5-year average cholesterols, who had a negative history for cardiovascular disease and a negative assay for lipid mobilizer factor. Blood serum and plasma samples were drawn prior to and 1, 10, 20, 40 and 60 minutes after the injection of heparin. The 6 post myocardial infarction cases started at values ranging from 3 to 7 mm., reaching a peak in 20 minutes of 12 mm. and falling to near pre-injection levels at 60 minutes, while the 6 normal pairs started between 8 and 14 mm., reaching a peak of 24 mm. in 20 minutes, with 60-minute values from 15 to 23 mm.

These preliminary findings suggest that the electrical activity of blood lipids may be of importance in studying proneness to myocardial infarction.

Atherosclerosis: Enhancement by Endothelial Activators

Denham Harman, Omaha, Nebr.

Atherosclerosis tends to occur in areas of injury (usually mechanical). Injury generally enhances tissue ability to take up particulate matter. Antihistamines inhibit this reaction to injury while it can be mimicked by so-called endothelial activators such as linalyl acetate. If serum lipids behave as particulate matter toward areas of aortic injury, then antihistamines might inhibit cholesterol-induced rabbit atherosclerosis; this has been demonstrated. Further, linalyl acetate and similarly acting compounds might enhance atherosclerosis. In this connection 2 experiments were conducted using 25 rabbits in each: 10 for controls and 5 each for treatment intramuscularly 2 times a week for 5 weeks with 30 mg./rabbit in the first and 60 mg./rabbit in the second of either linalyl acetate, citronellal or *d*-limonene dissolved in 1 cc. of olive oil. Each rabbit was given 100 Gm./day of a diet containing 1 per cent cholesterol and 5 per cent Wesson oil. After 5 weeks the rabbits were autopsied, aortas removed and stained with Sudan red and then graded on basis of 0 to 4+ atherosclerosis. The first experiment indicated that the treated animals developed more atherosclerosis than the controls and this was confirmed by the second: the average values for the atherosclerosis in the arch and thoracic aorta for the control, linalyl acetate, citronellal and *d*-limonene groups were respectively: 1.5 and 0.7, 1.8 and 0.6, 2.3 and 1.8, and 2.1 and 1.3.

These data support the hypothesis that aortic injury contributes to initial localization of lipid and subsequent development of atherosclerosis.

Aortic Lesions in Rabbits Treated with Bacterial Endotoxins

Thomas S. Harvey, DeWitt H. Smith, and A. Elizabeth Pikuzinski, Princeton, N. J.

In the course of pyrogen studies in rabbits receiving bacterial endotoxins, lesions in the media and intima of the ascending aorta and arch of aorta have been found to occur. Similar lesions, but of minimal degree, have been seen in four-sixteenths of the control rabbits, indicating other factors being involved in the genesis of the lesions, but the endotoxins play significant roles in increasing their severity. Nine-eighteenths of the treated animals showed greater than minimal lesions, 5 of which were marked lesions. The lesions consist of fragmentation of the elastic and collagen fibers and appearance of granulomas which, in their severe form, are partly calcified. Lipids are absent.

Origin and Fate of the Plasma Free Fatty Acid Mobilized in the Rabbit by Administration of Pituitary Fraction H (P)

Robert L. Hirsch, Daniel Rudman, Rosemary Ireland, and Ruth Skraly, New York, N. Y.

Fraction H from hog pituitaries mobilizes free fatty acid (FFA) into the blood of rabbits. The origin and fate of this FFA was studied by measuring arteriovenous differences in FFA concentration across various organs and tissues of normal rabbits and of rabbits receiving Fraction H.

All blood samples were obtained at laparotomy. Subcutaneous administration of glucose 1 hour earlier minimized the effect of operation upon FFA levels. In 10 control rabbits the arterial blood level of FFA was 150 to 390 μEq./L. The average FFA concentration in venous blood draining the perirenal fat pad was 88 μEq./L. less than in the arterial blood; average decreases of 51 μEq./L. were observed across the liver, and 68 μEq./L. across the kidney; insignificant increases occurred across the leg, and the intestines and mesentery.

One hour after subcutaneous administration of 1 mg. of Fraction H, plasma FFA concentrations in arterial blood were 600 to 2,800 μEq./L. FFA concentration of venous blood in these animals

increased an average of 465 μEq./L. across the perirenal fat pad, 120 μEq./L. across the leg, and 180 μEq./L. across intestines and mesentery. A reduction of 420 μEq./L. was found across the liver and 320 μEq./L. across the kidney. The same pattern prevailed in a group of animals examined 2 hours after injection. Stainable lipid was demonstrated histologically in hepatic cord cells and renal convoluted tubules of these animals.

It is concluded that administration of Fraction H mobilizes FFA into the blood from fat depots, and this FFA is removed from the blood during passage through the liver and kidney.

Atheromatous Lesions in the Hypothyroid Rat: Thiouracil vs. I^{131} Administration

Richard J. Jones, Chicago, Ill.

The basis for the idea that experimental myxedema enhances atherosclerosis rests largely upon experiments incorporating thiouracil feeding. There is some evidence that, when given in large doses, uracil drugs have more general cytotoxic effects than those confined to the thyroid gland. Boyd has suggested that the hypercholesterolemic effect of thiouracil is greater than expected from uncomplicated hypothyroidism. In view of these considerations, a comparison was made between adult rats fed a casein-lard synthetic diet and 2 per cent cholesterol, both with and without supplementary sodium cholate, and divided into: a control group (I); group II, which received an experimental dose of 0.25 per cent thiouracil; and group III which was given divided doses of I^{131}. Both hypothyroid groups had the same 4 months of exposure to serum cholesterol levels of 1,200 mg. per cent with and 600 mg. per cent without supplementary dietary cholate.

After sacrifice the aorta, heart, lungs, liver, kidney, testes, spleen, and thyroid were examined histologically. Except for the anticipated differences in appearance of the thyroid gland, initial histologic review revealed no striking differences among the groups. Early intimal thickening of the aorta and medial changes in the coronary and other small arteries were present in all groups. Scattered sudanophilic atheromatous lesions of the coronary arteries (all groups) and rare myocardial infarction (group III) were observed. While the hypothyroid provided perhaps more severe arterial lesions than the euthyroid rats, no difference was demonstrated between the lesions of the 2 hypothyroid groups.

Comparison of the Effect of Cigarette-Smoke Condensate and of Nicotine on Rabbits' Cardiovascular Tissue Cultures

Tatsuo Kokubu, O. J. Pollak, and Reizo Koide, Dover, Dela.

Ascending aorta and myocardium of normo- and of hypercholesteremic rabbits were studied. Nicotine solutions of varying strength and solutions of cigarette-smoke condensate were prepared. The strength of the latter solutions was adjusted according to nicotine content to allow comparison of results.

In experiments in which nicotine or smoke condensate was added to the nutrient medium prior to inoculation, the condensate proved more toxic than nicotine. It inhibited growth, thus fewer positive cultures were obtained after addition of smoke condensate than after addition of nicotine. Cell proliferation was similarly affected. Smoke condensate was also more toxic than nicotine when added 7 days after planting of the tissues. Growth curves were influenced more severely by the smoke condensate than by nicotine.

In the experiments concluded at this time, the character of morphologic alterations caused by cigarette-smoke condensate differed from the damage caused by nicotine. Increased granularity of the cytoplasm, nuclear pyknosis and ultimate cytolysis were noted in both series. Vacuolization prominent under the influence of nicotine was conspicuously absent from cells grown in nutrient medium with smoke condensate, in spite of comparable nicotine concentration.

In all experiments, endothelial cells were more sensitive than other aortic cells, and myocardial cells were more sensitive than aortic spindle cells.

Cigarette-smoke condensate contains, in addition to nicotine, other toxic substances. The question whether it also contains substances which neutralize, mitigate or modify the nicotine effect on rabbits' cardiovascular cells in vitro will be investigated.

Effects of Oxygen Tension on the Uptake of Labeled Lipoproteins by Human Atheromatous Plaques (P)

Abel Lazzarini-Robertson, Jr., New York, N.Y.

The uptake of tritium-labeled serum lipoproteins and protein-bound cholesterol 4-14C were studied in short-term organ cultures of human atheromatous plaques. Segments of the intima of the aorta, iliac, subclavian, mesenteric and coronary arteries, taken at surgery or shortly after death from patients with or without severe atherosclerotic lesions, were incubated in homologous nutrient under different concentrations of oxygen in a carbon dioxide-nitrogen mixture. The intracellular incorporation of labeled lipid was followed by differential centrifugation and determination of activity in different cell fractions, after ethanol-ether extraction, with a liquid scintillation counter.

The lipoprotein uptake was found to be inversely proportional to the oxygen tension of the gas

phase of the incubation chamber. Specimens from abdominal aorta, iliac and coronary arteries with advanced atherosclerosis were particularly affected by changes in oxygen concentration; their overall intracellular lipid incorporation ranged between 63.2 and 77.4 per cent above control preparations and was accompanied by a significant reduction of oxidative cell processes and increase in acid mucopolysaccharide production.

These results favor the concept that local anoxia of arterial intimal lining, as observed in vivo following parietal thrombi or arterial injury, may play an important role in the localization of lesions in human atherogenesis.

Detection of Preclinical Atherosclerosis: A Study of a Pair of Identical Twins

Robert S. Lees, and Frederick T. Hatch, Boston, Mass.

A pair of 27-year-old identical twins, 1 of whom had suffered a myocardial infarction, provided an unusual opportunity to search for premonitory signs of developing atherosclerosis. These men, extremely similar in personal history and habit, have a strong family history of coronary heart disease, but none of diabetes mellitus. They were grossly overweight, smoked heavily, and drank to excess. The asymptomatic twin was presumed to have a similar amount of atherosclerosis to his brother with the myocardial infarction. He was therefore studied intensively to detect evidence of developing atherosclerosis.

Tests of cardiovascular function, including electrocardiogram, exercise electrocardiogram, vectorcardiogram, and 1^{131}-Diodrast coronary blood flow, were within normal limits. Tests of carbohydrate and lipid metabolism were more revealing. Oral glucose-tolerance test showed an abnormally high peak followed by severe reactive hypoglycemia. This type of curve has been considered by others to be prediabetic. Serum cholesterol was 250 mg. per cent, considered high for the patient's age. Fasting serum triglyceride was distinctly elevated at 271 mg. per cent. Paper electrophoresis of fasting serum with staining for lipid revealed low α_1-lipoprotein, high β-lipoprotein, and the presence in abnormal amount of α_2-lipoprotein.

This study suggests that subtle but detectable abnormalities of lipid and carbohydrate metabolism exist before overt complications of atherosclerosis develop. The relationship of prediabetic glucose-tolerance test, hyperlipidemia, low serum α_1- and elevated serum α_2-lipoprotein to the occurrence of premature coronary atherosclerosis has been considered. The detection of these abnormalities may provide a rational basis for early institution of preventive measures in high-risk individuals.

Influence of Physiologic Factors (Autonomic Nervous System Activity) on Variability of Serum Cholesterol Concentration

Lena A. Lewis, Mohammed Moinuddin, and Irvine H. Page, Cleveland, Ohio

Single measurements of cholesterol concentration have come to be accepted as an important component of the "coronary profile." Too little attention has been paid to its physiologic variability. For this reason we studied in dogs the effect of high spinal cord section on the diurnal variations of cholesterol and total serum proteins. Further, the effects of a sympathetic blocking agent (guanethidine) were measured.

Hourly determinations several months after cord section showed the diurnal changes for both cholesterol and protein to be similar in normal and spinal dogs. The variations were irregular and unassociated with time of day or food intake and were much greater than those due to technical error of measurement, which was consistently $\pm$ 3 per cent or less. Blocking the sympathetic nervous system in cord-sectionized dogs and in normal dogs also did not change the diurnal pattern.

A correlation of high statistical significance existed between the diurnal changes in cholesterol and total protein in both normal and spinal dogs.

Serum cholesterol and total protein vary unpredictably from hour to hour with a range of cholesterol of $\pm$ 12 per cent from the mean and protein of $\pm$ 10 per cent. High spinal cord section and blockade of the sympathetic nervous system with guanethidine failed to abolish these variations. The sympathetic nervous system seems relatively less important compared with metabolic regulatory mechanism in the control of plasma cholesterol and protein levels.

Influence of Dietary Protein and Fat on Atherosclerosis in Resistant and Susceptible Pigeons

Hugh B. Lofland, Winston-Salem, N. C.

Previous results from this group suggested that diets high in casein were more atherogenic for White Carneau pigeons than were diets low in protein. In an extension of these experiments, pigeons susceptible or resistant to atherosclerosis (White Carneau or Show Racer respectively) were maintained for 6 months on diets containing a protein of vegetable origin (alpha-protein from soybean), fed at 2 levels, and either 1 per cent or 15 per cent corn oil. In addition, all birds received 0.25 per cent cholesterol in the diet.

In agreement with our results using casein, diets high in protein resulted in more extensive atherosclerosis than did diets low in protein, but only in the susceptible breed—i.e., high-protein

diets do not overcome the natural resistance of Show Racer pigeons. Serum cholesterol levels were not significantly affected by protein, but were significantly reduced when the diet contained 1 per cent corn oil as contrasted to 15 per cent.

In these experiments it was also observed that White Carneau pigeons in certain dietary groups developed severe symptoms of thiamine deficiency, despite the presence of thiamine in the diet. Show Racers did not develop such deficiency, suggesting that the breed of pigeon susceptible to atherosclerosis is also susceptible to thiamine deficiency. The susceptible pigeons developed thiamine deficiency only when the dietary protein was from soybeans, never during the casein-feeding experiments. The relationship of these observations to atherosclerosis has been considered.

Blood Viscosity in "Normal" and Coronary Subjects (P)

George A. Mayer, and W. Ford Connell, Kingston, Ontario, Canada

While the factors governing blood viscosity are still poorly understood, this property of the blood is of undoubted importance in governing the volume and velocity of blood flow. The healthy, elastic vascular system is well equipped to cope with normal variations in blood viscosity. However, vessels rendered inelastic and narrowed by disease have little or no adaptive capacities. In such circumstances, changes in blood viscosity may become of critical importance in determining the blood supply to certain vital areas.

With an apparatus designed by us, the viscosity of whole blood and of plasma, relative to that of distilled water, has been measured with a high degree of reproducibility. The standard error of our method is ± 0.5 per cent.

(1) In 30 healthy children of both sexes, aged 3 to 10 years, the relative blood viscosity (RBV) was 3.28 and the relative plasma viscosity (RPV) 1.51. (2) In 30 healthy female subjects, aged 20 to 25 years, the mean RBV was 3.35 and the RPV 1.53. (3) In 21 healthy male subjects, aged 20 to 24 years, the mean RBV was 3.87 and RPV 1.62. (4) In 15 healthy male subjects, aged 40 to 60 years, the mean RBV was 4.14 and RPV 1.62. (5) In 30 male and 6 female subjects with chronic coronary heart disease, the mean RBV was 4.38 and RPV 1.69.

The significantly higher whole blood and plasma viscosity may well be a major factor in the reduction of blood flow and in the production of clinical symptoms in patients with advanced coronary atherosclerosis.

Hormonal Correction of Physiologic Hypercholesterolemia (P)

Campbell Moses, Thaddeus S. Danowski, John R. Jablonski, Joseph H. Sunder, and Jean H. Greenman, Pittsburgh, Pa.

The administration of 10 to 20 mg. of hydrocortisone to 40 normal men was followed by a significant decrease in the excretion of urinary 17-ketosteroids and a fall in the level of the total serum cholesterol. This suggests that the physiologic hypercholesterolemia of middle-aged men in part results from the effects of the androgenic steroids elaborated in response to pituitary adrenocorticotropin and that the administration of appropriate doses of hydrocortisone may correct this abnormality.

The addition of 130 to 195 mg. of desiccated thyroid to this regimen increased the hypocholesterolemic effect produced by hydrocortisone administration. The decrease in total serum cholesterol was due to a decrease in the beta-lipoprotein cholesterol. No significant changes in the alpha- and beta-lipoprotein partition of triglyceride or lipid phosphorus were observed.

This hypocholesterolemic response was sustained for 2 years without discernible change in any of the clinical, biochemical or physiologic parameters examined.

Dietary Fat and Platelet Survival in Man (P)

J. Fraser Mustard, Toronto, Canada, and Edmond A. Murphy, Baltimore, Md.

There is considerable published evidence that certain dietary fats enhance blood coagulation. Almost all of these studies have been acute and concerned with in vitro tests.

A study was undertaken in 7 men in a metabolic unit in which they received diets containing: (1) egg yolk and dairy fats, (2) vegetable fat, and (3) little fat, respectively, during 3 periods of 5 weeks. As well as the use of in vitro tests of coagulation (platelet adhesiveness, platelet clumping, factor IX assays), platelet survival and turnover were estimated by P^{32}-labeled diisopropylfluorophospate as an in vivo measure of coagulation. Blood cholesterol and phospholipid values were also followed.

In all 7 subjects, platelet survival was shortest, and platelet turnover greatest, during the period of diet containing egg yolk and dairy fat. In vitro coagulation test showed a less definite but similar trend. Converse results were obtained during the administration of the low-fat diet, and intermediate values during ingestion of vegetable fat. The cholesterol and phospholipid values were similar in the low-fat and vegetable-fat periods,

but significantly higher during the egg-yolk, butter-fat period. These results show that dietary fats which are known to increase the serum cholesterol also have the most marked effect on coagulation as measured by in vivo tests. This latter effect is on the early stages of clotting and shortens platelet survival.

Blood Coagulation and the Formation of Deposits in Extracorporeal Shunts

J. Fraser Mustard, Toronto, Canada, Edmond A. Murphy, Baltimore, Md., Harry G. Downie, and Harry C. Rowsell, Guelph, Ontario, Canada

We have shown the analogy between the topography and histochemistry of deposit formation in models of various vessel configuration when placed in extracorporeal circulations in swine, and the early stages of atherosclerosis. In addition to alterations in blood flow, the nature of the blood is important in the formation of the deposits. The encrustation can be quantitated by weighing the deposit formed following flow for a fixed period of time in a standard system.

We have used this to study the effect of altering the character of circulating blood on the formation of these deposits. It has been found that in moderate doses dicumarol (prothrombin time 1 to 1.5 times normal) significantly increases the amount of deposit formed, while in high doses (prothrombin time greater than twice normal) there is a reduction. In experiments started 10 minutes after administering 10,000 units of heparin, no deposit forms. Shunts started when the clotting time returns to normal show a 4-fold increase in deposit. This evidence indicates that altering coagulability alters the amount of encrustation.

The effect of diet was studied in 4 groups of 6 pigs. Pigs receiving lard (23 per cent of calories), egg yolk (23 per cent of calories) or lard and cholesterol (23 per cent of calories) showed significantly more deposit formation than animals on a low-fat diet. The mean weight of deposit formed in the egg- and lard-fed pig shunts was 7 times that in the control animals. This evidence indicates that diets rich in fat increase the amount of encrustation.

Effect of Nicotinic Acid on Human Cholesterol Biosynthesis (P)

Stewart L. Nunn, W. Newlon Tauxe, and John L. Juergens, Rochester, Minn.

A possible mechanism by which nicotinic acid decreases the plasma cholesterol concentration is biosynthetic inhibition. To test this hypothesis we studied the conversion of C^{14}-acetate to C^{14}-cholesterol in 9 nondiabetic humans before and 2 weeks after the daily administration of 3 to 6 Gm. of nicotinic acid. The amount of plasma C^{14}-cholesterol present at the peak time after intravenous injection of C^{14}-acetate was arbitrarily used as an index of cholesterol biosynthesis.

Seven of the patients did not change their diet during the study. Six of these responded to nicotinic acid therapy with an average reduction in cholesterol biosynthesis to 50 per cent of pretreatment values. The plasma cholesterol concentration was reduced in all 6 patients by an average of 32 per cent from pretreatment concentrations. In the seventh patient neither cholesterol biosynthesis nor plasma cholesterol concentration changed.

Two patients changed to a low-fat diet at the time nicotinic acid therapy was started. In contrast to the first group, the plasma radiocholesterol appearance peaks increased in these patients by 24 and 273 per cent respectively, even though the plasma cholesterol concentration was reduced in both instances. Our experience with dogs indicates that an increase in cholesterol biosynthesis occurs when the saturated fat in the diet is decreased. It is possible that in these 2 patients a similar effect of the low-fat diet outweighed the biosynthetic inhibition observed in most patients treated with nicotinic acid who had no change in diet.

Reduction in Hepatic Synthesis of Cholesterol from C^{14}-Acetate in Hypercholesteremic Patients by Nicotinic Acid (P)

William B. Parsons, Jr., Madison, Wis.

Carbon^{14}-acetate has been administered orally (100 to 200 μc.) to hypercholesteremic patients while receiving nicotinic acid (1.0 to 2.0 Gm. 3 times daily) and again during a control period while they received either an equal dose of nicotinamide or a placebo. Incorporation of specific radioactivity into serum free and esterified cholesterol and into erythrocyte cholesterol was measured, using the Gould technic.

The curves during nicotinic acid administration are similar to Gould's values in patients with normal cholesterol levels. On nicotinamide or a placebo, the same patients show much higher peaks of specific activity in all fractions, with otherwise normal relationship and equilibration of the curves. These observations are consistent with the finding of decreased cholesterol synthesis and increased conversion of acetate to carbon dioxide in rat-liver preparations (Perry; Gamble and Wright). Collection of expired air for labeled carbon-dioxide determinations has been included in further experiments in this study, but data are not available at the time of submission of this

abstract. The effect of nicotinic acid on incorporation of mevalonic acid into cholesterol will also be studied, to localize the point of synthesis inhibition, which in rat-liver homogenates has appeared to be between acetate and mevalonate (Gamble and Wright).

These data in humans strongly suggest that reduction in serum cholesterol and disappearance of visible deposits of tissue cholesterol (xanthoma tuberosum, xanthoma tendinosum, xanthelasmas) during nicotinic-acid therapy result, in part at least, from marked reduction in hepatic synthesis of cholesterol.

Effect of Isolation on Cholesterol-induced Atherosclerosis in Cockerels

Ruth Pick and Louis N. Katz, Chicago, Ill.

Many factors are known to influence the production and regression of hypercholesterolemia and atherosclerosis. The most extensively studied are diet, hormones and drugs. Experimental work on emotional and environmental factors influencing diet-induced atherosclerosis is scanty. Therefore, a program was begun to evaluate the effect of disturbances of living conditions on this disease. Cockerels were used because they form a social (pecking) order much like man's. The effect of disturbances in pecking order was studied on the induction and regression of cholesterol-oil-induced aortic and coronary atherosclerosis. The results showed that disturbing the pecking order within the normal environment of a large chicken room had no demonstrable influence on atherogenesis, but produced masculinization as evidenced by testes weights.

Isolation of groups of animals in a quiet room, separated from the other birds, produced significant changes in the degree of atherogenic response to the diet in the thoracic aorta (controls 1.44, isolated 1.85; $P < .01$) and coronary arteries (controls 21.9, isolated 32.4; $P < .001$). Also, regression of coronary lesions was significantly retarded (controls 12.9, isolated 23.4; $P < .001$). The isolated birds also showed significantly depressed comb and testes growth.

These experiments indicate that environmental stimuli, possibly acting by way of emotional factors, may modify the response to an atherogenic diet. Whether this is mediated by nervous or hormonal factors is being investigated.

Lipogenic and Cholesterogenic Activities of Simple Dietary Triglycerides (P)

Raymond Reiser, Mary C. Williams, Mary F. Sorrels, and Nadella L. Murty, College Station, Texas

Simple saturated triglycerides, from tributryn to tripalmitin, as well as triolein and trilinolein, were fed to 200 Gm. rats as 30 per cent of their rations, by weight, for 2 weeks. At 8 A.M. on the day of the test they were injected intraperitoneally with 0.2 mc. of 1-C^{14} sodium acetate per Kg. of body weight. One hour later they were sacrificed.

The percentage of injected acetate incorporated into liver fatty acids decreased with increase in molecular weight and degree of unsaturation of the dietary fat, from 7.5 per cent on the fat-free to 0.2 per cent on the trilinolein diets. The degree of incorporation of acetate in liver cholesterol was between 0.07 and 0.1 per cent on the fat-free and all fat diets except tripalmitin and trilinolein. After tripalmitin ingestion, it was approximately 0.3 and 0.6 per cent in each of 2 groups respectively, and after trilinolein only 0.04 per cent. The liver cholesterol level of animals on the fat-free diet was slightly over 2 per cent. This value rose to between 4 and 5 per cent in the livers of animals receiving saturated fats and triolein, and to over 7 per cent in those ingesting trilinolein.

The activity of labeled cholesterol into the aorta was well over 100 cts./min./mg. in all animals except those fed tripalmitin, in which case it was only 24 cts./min./mg., suggesting a slow transport of cholesterol into the aorta by animals ingesting palmitic acid. In contrast, much higher levels of labeled cholesterol in the aorta of swine fed myristolaurin than in those fed cottonseed oil, 24 hours after 1-C^{14} acetate administration, suggest that the slow transport of cholesterol into the aorta of animals ingesting saturated fat is accompanied by an even slower rate of transport out of it.

Thrombosis and Cardiac Infarct in the Rat Kept on a Simplified Diet

Serge Renaud, Claude Allard, and Gaston Choquette, Montreal, Canada

A few semi-synthetic diets have been devised for producing thrombosis and cardiac infarct in the rat. Since these diets induce a very small percentage of cardiac infarcts, the possibility exists that certain unexpected factors contained in natural food could be important in this cardiovascular disease. Therefore, we utilized Purina Laboratory Chow to which were added some factors suspected to play a prominent role in atherosclerosis and thrombosis.

Male rats of the Sprague-Dawley strain (Quebec Breeding Farm), weighing 120 Gm., were placed on the following diet: Purina laboratory chow (53 per cent), cholesterol (5 per cent), cholic acid (2 per cent), and butter (40 per cent). These rats grew almost normally, were in good shape, but died in an average of 6 months of cardiac infarcts in a proportion of about 80 per cent. These infarcts,

caused by thrombosis, were generally small, multiple and disseminated all over the heart. Occasionally, they were large and involved the entire left ventricle. Usually, only the myocardial fibers were affected and presented the different degenerative stages already described after coronary ligation.

Feeding this diet produced in the serum permanent changes: total cholesterol and total lipids rose gradually to very high levels, while the percentage of alpha-lipoproteins decreased. Addition of propylthiouracil to the diet increased dramatically the hypercholesterolemia and hyperlipemia, but the life duration of the rat was reduced to 50 days as a mean, and the percentage of cardiac infarcts, to about 30 per cent.

Distribution and Severity of Spontaneous Atherosclerosis in the Dog (P)

James C. Roberts, Jr., Torrance, Calif.

Detailed morphologic studies have been made of the aortas, coronary arteries, and hearts of 405 dogs dying from various causes in eastern Tennessee or southern California. Data concerning diet, temperament, age, breed and habitus of these pets were also obtained.

Emphasis is placed on: (1) presence of minimal but definite lesions in the aorta at an early age; (2) the similarity of these lesions to early human lesions; (3) slight progression and no complication of these lesions with increasing age, in contrast to human lesions; (4) the lack of myocardial disease in old dogs; (5) the minimal effects of obesity, sex difference or other factors currently implicated in human disease.

Some Factors Affecting the Rate of Regression of Hypercholesteremia During "Unloading" Diets in the Chick

Simon Rodbard and Christine B. Williams, Buffalo, N. Y.

After induction of hypercholesteremia in chicks by a short period of cholesterol feeding (loading), the return to a normal mash (unloading) diet was followed by an exponential fall of the plasma cholesterol level. The rate of fall was markedly affected by changes in the dietary pattern or in the hormonal status of the chick. Thyroidectomy or thiouracil administration at the onset of the unloading period slowed the fall; thyroid administration accelerated the return to normal. Neither dinitrophenol nor triiodothyronine affected the unloading process. The fall in plasma cholesterol was delayed in accord with the degree of caloric restriction. Addition of cholesterol supplements of as little as 0.1 per cent to the unloading diet slowed the rate of removal of excess cholesterol from the plasma; the rate could be restored to normal by concurrent feeding of soy sterols or safflower oil, but not by the feeding of corn or coconut oils. These data indicate that the processes of loading and unloading operate through different mechanisms, responses to the unloading process being more definitive and quantitative than responses to equivalent loads.

The Formation of Lipoproteins by the Isolated Perfused Rat Liver (P)

Paul S. Roheim and Howard A. Eder, New York, N. Y.

When the livers from cholesterol-fed rats were isolated and perfused with whole blood, the cholesterol concentrations of the perfusate increased by 25 to 30 per cent and reached a maximum value in about 90 minutes. However, when perfusion was continued with replacement of fresh blood, further release of cholesterol occurred. When Ringer's solution was substituted for the plasma of the perfusing fluid, the release of cholesterol was *ca* 25 per cent of that observed with whole blood.

Perfusions were carried out using, as the perfusing fluid, plasma from which the lipoproteins had been removed by ultracentrifugation at D 1.21 and to which were added washed red blood cells; the release of cholesterol was similar to that observed in perfusions with whole blood. Phospholipids and triglycerides were also released into the perfusate. Most of this lipid was found in a very low density ($D < 1.019$) lipoprotein fraction, although small amounts of D 1.019 to 1.063 and D 1.063 to 1.21 lipoproteins were found.

A similar experiment was carried out in which the proteins of $D > 1.21$ were labeled by injecting the blood-donor rats with C^{14}-labeled chlorella hydrolysate. When the lipoproteins were separated from the "plasma" of the perfusing blood, it was found that the newly formed $D < 1.019$ lipoproteins had a specific activity that was higher than that of the original $D > 1.21$ proteins and considerably higher than that of the other 2 lipoprotein fractions.

These findings suggest the presence of protein in the $D > 1.21$ fraction which serves as an efficient precursor of lipoproteins.

Study of the Possible Effect of Gainful Employment on Serum Cholesterol, and Incidence of Hypertension, Arcus Senilis, and Clinical Coronary Heart Disease in Urban American Females

Ray H. Rosenman, Meyer Friedman, and Vernice Carroll, San Francisco, Calif.

Urban American males now fail to exhibit oc-

cupational differences of coronary disease morbidity prevailing in England and elsewhere and formerly in the United States. In order to study possible effects of occupational "time pressures" and other stresses unique to gainful employment per se in a large urban area, 2 groups of white females, aged 30 to 59 years, were randomly selected for us by several lay female selectors who believed each selected subject to be entirely in good health. Group A consisted of 117 white-collar workers and business executives, and group B of 97 housewives not gainfully employed. History, height, weight, blood pressure, duplicate serum cholesterol, presence of arcus senilis, electrocardiogram (interpreted "blind" by an independent electrocardiographer) and diet diary carefully recorded for 7 days (calculated "blind" by a dietician) were obtained.

Comparative findings in groups A and B respectively were: (1) diastolic pressure exceeded 95 mm. Hg in 23 and 8 per cent; (2) arcus senilis found in 32 and 10 per cent; (3) clinical coronary disease (by history and/or electrocardiogram) found in 14 and 5 per cent; (4) average serum cholesterol was 270 ± 3.5 and 225 ± 3.7 mg./100 ml. These striking differences prevailed in each paired subgroup of subjects subdivided by age decade, and were not found ascribable to any differences of average age, height, weight, catamenia, menopause, physical activity or diet.

On the Mechanism of the Reduction of Serum Cholesterol Concentrations by Neomycin in Man

Paul Samuel, New York, N. Y.

It has been reported that daily oral administration of 1.5 to 2 Gm. of neomycin significantly reduced serum cholesterol in man. Daily intramuscular injections of 60 mg. failed to alter serum cholesterol. In this study 14 patients received oral or intramuscular neomycin, while concentrations of the drug were determined serially in serum, urine and bile. Radioactive fat-absorption studies were made in 4 additional subjects whose serum cholesterol was reduced by neomycin administration.

One oral dose of 2 Gm. of neomycin resulted in average peak serum concentrations of 0.28 μg./ml. in 5 patients; only traces of neomycin were noted in the serum of 3 patients receiving 2 Gm. in divided doses. Intramuscular injections of 60 mg. of neomycin to 5 subjects produced average peak serum concentration of 3.4 μg./ml. without lowering cholesterol. Average urinary excretions were 0.4 and 37.5 per cent respectively. In 4 patients, who received 2 Gm. of neomycin orally, T-tube bile contained traces of the drug in 3 patients and an average of 1.5 μg./ml. in the fourth. Sixty mg. of intramuscular neomycin resulted in appreciable serum, urine and bile levels (0.3 to 1.8 μg./ml.) of the drug. Radioactive fat-absorption studies, during control periods and following the reduction of cholesterol by neomycin, demonstrated complete absorption of I^{131}-labeled triolein during all periods.

The data indicate that the cholesterol-lowering effect of neomycin depends upon its activity in the gastrointestinal tract. It is independent of dietary fat absorption and on enterohepatic circulation of the drug, which is absent. Its mechanism of action may be mediated via changes in the intestinal bacterial flora or intestinal enzyme systems.

Fatty Acids of Adipose Tissue and Plasma Lipids of Guatemalan and North American Nondiabetics and Diabetics

Robert F. Scott, Kyu T. Lee, Albany, N. Y., and Carlos Tejada, Guatemala City, Guatemala

Poor urban and rural Guatemalan nondiabetics have been reported to have less arteriosclerosis than comparable North Americans. Fatty acids of adipose tissue and plasma lipids were compared in age- and sex-matched subjects from these groups; adipose-tissue fatty acids were measured because in part they reflect the dietary intake of fatty acids. Because of the high occurrence of myocardial infarcts in diabetics, at least in North America, Guatemalan and North American diabetics were compared as separate groups.

Of the 6 fatty acids measured and compared, the relative percentage of oleic acid was significantly lower and palmitoleic acid higher in Guatemalan than in North American nondiabetics; plasma cholesterol and esterified fatty acids were lower in the Guatemalan nondiabetic group. Comparison of Guatemalan and North American diabetics showed no significant differences in either plasma lipids or in adipose-tissue fatty acids.

The differences in adipose tissue composition suggest that the type of fatty acid consumed by the nondiabetic Guatemalan may be slightly different from that consumed by comparable North Americans, but the wide difference in arteriosclerosis between the 2 groups is more likely explained by the reported great difference in the quantitative fat intake between Guatemalan and North American diabetics. The absence of either plasma lipid or adipose-tissue fatty acid differences between Guatemalan and North American diabetics suggests that the Guatemalan diabetic either has a different dietary fat intake than the Guatemalan mondiabetic, or that he reacts differently to the same diet. In view of the findings reported herein, it will be of considerable interest to find out the degree of arteriosclerosis in this group.

Serum Lipoprotein Parameters in the Newborn (P)

Ronald L. Searcy, Vincent P. Carroll, Jr., Jane V. Hamilton, Geraldine Y. Dyer, and Lois M. Bergquist, Los Angeles, Calif.

Heretofore serum requirements have precluded extensive analysis of lipoproteins in infants by methods other than electrophoresis. Development of a specific antiserum (Hyland) permits estimations of lipoproteins (density $<$ 1.063 Gm./ml.) by immunoprecipitation in only 30 μl. of serum. Measurements of precipitate columns in standardized microcapillary tubes compared favorably ($r = 0.659$) with 123 ultracentrifugal analyses of S_f 0-400 lipoproteins. Immunochemical technics were used to estimate low-density lipoproteins as well as total, alpha- and beta-lipoprotein cholesterol in capillary blood from 456 healthy infants one-half hour to 53 days of age. Analyses were performed on several occasions so that evaluations could be made on an individual as well as a group basis.

During the first 24 hours postpartum, infants exhibit very low levels of serum low-density lipoproteins. Estimations of hemoconcentration suggest that total circulating amounts of this lipoprotein fraction are actually much less than observed values indicate. Striking neonatal elevations in serum low-density lipoproteins occur during the first month of life despite considerable expansions in plasma volume. However, 10 to 30 days after birth, low-density lipoprotein values remain far below the mean of 2.8 $\pm$ 0.08 mm. (95 per cent confidence limits of the mean) observed in 501 healthy adults. In contrast, serum total cholesterol levels and beta to alpha lipoprotein cholesterol ratios approach adult ranges during the first month of life. These data suggest that there are differences in neonatal metabolism of glyceride-bearing as opposed to cholesterol-bearing molecules in the low-density lipoprotein spectrum.

Hypolipemic Effects of D-Thyroxine Therapy in Coronary Patients

Ronald L. Searcy, Joseph S. Carlucci, and Lois M. Bergquist, Los Angeles, Calif.

Over a 3-month period, 34 subjects with clinical coronary artery disease were given increasing oral doses of D-thyroxine up to 8.0 mg. per day. Medication was well tolerated in all patients, including those with severe angina pectoris. Serum total, alpha- and beta-lipoprotein cholesterol were estimated immunochemically before treatment and biweekly thereafter. After 3 months, reductions in serum total cholesterol ranging from 25 to 275 mg. per cent were observed in 27 patients. These decreases were largely confined to the beta-lipoprotein fraction. Absolute increase in alpha-lipoprotein cholesterol occurred in 13 subjects, but a majority of the study group showed depressions in beta/alpha lipoprotein ratios.

Lipoproteins (density $<$ 1.063 Gm./ml.) were estimated in mm. of immunoprecipitate sedimented in capillary tubes. These measurements compare favorably ($r = 0.659$) with ultracentrifugal analysis of S_f 0-400 lipoproteins. Pretreatment levels of lipoprotein precipitate in coronary patients averaged 3.6 $\pm$ 0.27 mm. (95 per cent confidence limits of the mean). This value was significantly higher ($P < 0.001$) than a mean of 2.8 $\pm$ 0.08 mm. (95 per cent confidence limits of the mean) observed in 501 clinically healthy subjects. At the end of 3 months, 19 patients receiving D-thyroxine showed reductions in precipitate ranging from 0.2 to 2.0 mm. The decrease did not always parallel changes in beta-lipoprotein cholesterol.

These preliminary data suggest that D-thyroxine can be used to effectively reduce serum total and beta-lipoprotein cholesterol as well as low-density lipoproteins in patients with severe coronary artery disease.

Genetically Determined Variant of Human Beta-Lipoprotein (P)

Winnifred Seegers, Lee B. Weiner, and Kurt Hirschhorn, New York, N. Y.

Studies of human serum lipoproteins have in the past been chiefly concerned with quantitative variations and their clinical significance. Recent reports of families in whom a normally present lipoprotein fraction was absent or present only in decreased amounts have suggested that there is a simple genetic basis for the production of the protein fraction of these lipoproteins.

We have studied a family in which a qualitative variant of serum beta-lipoprotein appears. This abnormality is seen in electrophoretic patterns as a "split" $beta_1$-lipoprotein band with 2 distinctly separated components, 1 of slightly increased mobility relative to the $beta_1$ band of pooled control serum, and 1 of slightly decreased mobility. This "split" band occurs in family members of 3 generations, ranging in age from 4 to 76 years, and has no apparent association with clinical disease. Total serum cholesterol is slightly elevated in the majority of individuals with the abnormal pattern. Ultracentrifugal fractionation of serum from the propositus reveals only a slight elevation of $beta_1$-lipoprotein cholesterol (S_f 0-16). Interpretation of the relationship of abnormal cholesterol levels to the electrophoretic variant is made difficult by the independently introduced hyperlipemia with secondary hypercholesterolemia which occurs in some members of this family.

The familial occurrence of this variant adds to the evidence for genetic control of the production of lipoproteins. If the protein involved in a lipoprotein complex is under direct genetic control, detection of additional variations due to molecular changes in the protein may be expected.

Sustained Incidence of Cardiovascular Disease in a Population with Decreased Blood Cholesterol Levels

Daniel A. Sherber, New Rochelle, N. Y., and Martin Marcus, New York, N. Y.

Prompted by a gradually increasing difficulty in obtaining patients with hypercholesterolemia (blood levels over 300 mg./100 ml.) for experimental studies, a survey of blood-cholesterol levels on 1,000 recent hospital admissions was made and compared with a similar study made in 1953 in the same laboratory by the same method (Abell). The following facts were elicited: (1) the incidence of hypercholesterolemia is now about 4 per cent as compared with 13.7 per cent in 1953; (2) the number of admissions to the medical service with cardiovascular disease has not changed and is about 50 per cent of the total in this city hospital; (3) a notable shift in blood-cholesterol levels has occurred, so that many values below 150 mg./100 ml. are now in evidence, although rare in the original study; (4) blood cholesterol levels increase with age through the fifth decade and then level off. Values for the third through the eighth decades are all lower than previously observed.

Several factors may account for these observations: (1) there has been an increased number of nonwhite admissions at the expense of the white group, corresponding to a shift in the ethnic origins of the population served by the hospital; (2) an increasing public diet-consciousness may be causing a shift in dietary habits to foods considered by some to be less cholesterogenic; (3) factors such as hypertension and stress may be taking their toll in spite of blood-cholesterol decreases.

The significance of the continued occurrence of cardiovascular disease in the face of decreasing blood cholesterol is self-evident.

Search for Atherogenic and Anti-atherogenic Substances

Takio Shimamoto, Toshiaki Sunaga, Tadahiro Sano, Isamu Yagishita, and Tadayuki Hiroki, Tokyo, Japan

We found (1959) that various fatty and nonfatty substances were capable of inducing "stickiness" of arterial endothelial cells. This resulted in the adherence of platelets and leukocytes to the intima. This immediate reaction produced "atherosclerosis" which corresponded morphologically to the "fatty spots or streak" of man as defined by the W.H.O. in 1958. In long-term studies, the reaction occurred also in animals kept on a low-fat diet. We also found that monoamine oxidase-inhibitor prevents the phenomenon of endothelial stickiness and platelet-leukocyte adherence which could be commonly induced by various atherogenic substances, such as epinephrine and cholesterol.

In this experiment it was found that aortic atherosclerosis induced in 60 rabbits by daily cholesterol feeding of 2 to 5 Gm. was minimized ($P < 0.02$) by concomitant administration of nialamide in a dose of 5 mg. per Kg. This treatment was capable of preventing the intimal surface phenomenon induced by cholesterol although nialamide did not lower the blood cholesterol level of the animals.

Study of substances which induce stickiness of endothelial cells seems important to elucidate atherogenesis. Using technics of direct microscopic observation of blood vessels of rabbits' mesentery or ear (Sandison-Clark) in vivo and of platelet counting (Olef) as well as adhesive-platelet counting (Moolten), various fatty substances administered orally in doses of 1 to 2 Gm. per Kg. were tested. Cholesterol, lanolin, butter, lard, butyric acid and stearic acid induced stickiness. Oleic acid had but slight effect. Soybean oil, safflower oil and linoleic acid did not affect the vascular endothelium of rabbits.

Frequency of Isolated Segmental Coronary Occlusion (P)

David M. Spain, Brooklyn, N.Y., Victoria A. Bradess, Pedro T. Iral, and Antonia G. Cruz, Valhalla, N. Y.

A detailed study was made of the degree and extent of coronary atherosclerosis and luminal narrowing in the 3 main coronary arteries by both dissection and injection technics on 100 hearts from males who had died suddenly from advanced coronary atherosclerosis, and on 100 males who had died from accidental causes. In those individuals who had died from coronary artery disease, isolated segmental coronary occlusion was not found. The process was always diffuse with multiple segmental areas of more advanced narrowing. In every instance at least 2 of the 3 major branches revealed extensive and diffuse changes. In those individuals who had died from accidental death, isolated atherosclerotic plaques were found. As the degree of the atherosclerosis increased, the process became less isolated and less segmental.

These findings bear upon the pathogenesis of ischemic heart disease and favor atherosclerosis as opposed to thrombosis as the basic process.

Thrombosis was never found except in the presence of moderate to advanced atherosclerosis. These findings also indicate that certain surgical procedures recently advocated for coronary occlusion would be of extremely limited value.

Myocardial Uptake of Free Fatty Acids in Normal, Atherosclerotic and Hypothyroid Dogs, Before and During Hypoxia and the Administration of Norepinephrine or Insulin

John J. Spitzer, Lawrence J. Finkelstein, and John C. Scott, Philadelphia, Pa.

In an effort to extend our previous studies, the effects of atherosclerosis (i.e., radioiodine thyroidectomy and cholesterol feeding for at least 1 year), hypothyroidism, hypoxia, norepinephrine and insulin were studied on the myocardial uptake of free fatty acids (FFA). The uptake of FFA was determined from A-V (artery-coronary sinus), FFA differences and coronary blood flow data.

Atherosclerotic dogs showed elevated arterial FFA levels, normal A-V differences, coronary flow and FFA uptake, and diminished extraction (A-V/A) of FFA. Hypothyroidism without subsequent cholesterol feeding lowered the myocardial uptake of FFA, as a result of decreased A-V differences. The arterial level remained unchanged.

Hypoxia (breathing a mixture of 10 per cent O_2 and 90 per cent N_2 for 1 hour) in normal dogs raised FFA uptake, arterial level and coronary flow. In hypothyroid animals the same mixture did not influence the already lowered myocardial uptake of FFA, but did lower A-V differences and thus extraction of FFA. Coronary flow was increased.

Infusion of norepinephrine increased myocardial uptake mostly by increasing coronary flow. Although arterial FFA level almost doubled, the change in A-V differences was not significant. Fifteen minutes after the administration of 0.5 units/Kg. of insulin, the well-known decrease of the arterial FFA was accompanied by a diminished A-V difference. Neither coronary flow nor FFA uptake changed significantly.

Dietary Changes and Serum Cholesterol Responses in Coronary-prone Middle-aged Men Participating in a Coronary Prevention Evaluation Program (P)

Jeremiah Stamler, Yolanda Hall, David M. Berkson, and Quentin D. Young, Chicago, Ill.

In mid-1958, a long-term study was launched to assess ability to prevent clinical coronary heart disease by nutritional-hygienic means in free-living volunteer high-risk men age 40 to 59. Men assessed as coronary-prone are those with hypercholesterolemia, hypertension, obesity (any 2 or all 3), and/or nonspecific ST-T abnormalities on electrocardiogram. A majority had the combination hypercholesterolemia and obesity. Recommended nutritional changes emphasized low intake of saturated fat, cholesterol, refined carbohydrate; moderate intake of total calorie, total fat, polyunsaturated fat; high intake of protein and other essential nutrients. Frequent assessment was made of serum cholesterol and diet, evaluated from 7-day food records, analyzed by IBM methods. Of the participants with hypercholesterolemia, 76 per cent manifested a fall in serum cholesterol of 10 per cent or greater; the mean change in the responders was 22 per cent (306 mg. per cent to 238). Fall in serum cholesterol correlated best with intake of saturated fat, reduced to 15 Gm./day, 8 per cent of total calories. Participants exhibiting no fall in serum cholesterol reported food records with higher intake of saturated fat and cholesterol than the responders. Failure of serum cholesterol to decline in men adhering satisfactorily to nutritional recommendations was estimated to occur in less than 10 per cent of men. A nutritional approach to long-term correction of hypercholesterolemia in an effort to prevent clinical coronary heart disease is feasible in a majority of free-living middle-aged male volunteers.

Importance of Dietary Cholesterol (P)

Alfred Steiner, Elliott Howard, and Suat Akgun, New York, N. Y.

The failure of the addition of large amounts of crystalline cholesterol to the diet of man to significantly alter the serum cholesterol level has led to the generally accepted concept that dietary cholesterol plays little or no role in the production or maintainance of hypercholesterolemia. Egg-yolk powder containing 3 per cent cholesterol has been shown to cause a significant elevation of the serum cholesterol level of man, while crystalline cholesterol was largely ineffective. Differences in absorption of cholesterol from the gastrointestinal tract explained the divergent results.

This problem has been restudied in 6 patients, using the formula diet technic. After an initial control period, the patients were placed on a formula diet (carbohydrate 220 Gm., protein 70 Gm., fat 90 Gm.) made up of skim milk, dextrose, and olive oil for 4 weeks. Three Gm. of crystalline cholesterol daily were then added to the formula diet for 8 additional weeks. It has been demonstrated that a maximum increase in the serum cholesterol level from 61 to 136 mg. per cent (mean 82 mg. per cent), or from 23 to 48 per cent, occurred when the cholesterol was added to the formula diet as compared to values obtained during previous control periods.

A re-evaluation of the importance of the cholesterol content of the diet appears warranted.

Role of the Macrophage in Experimental Atherosclerosis (P)

W. J. S. Still, Robert C. Simon, and Robert M. O'Neal, St. Louis, Mo.

The essential arterial lesion produced in animals by feeding cholesterol is an intimal collection of fat-filled macrophages. The present study was designed to clarify some of the problems on the origin of these cells and the mechanisms by which they accumulate.

It was found that rats fed various high-fat diets contained in their blood numbers of vacuolated macrophages similar to those seen in their aortic intimas. A method was devised to satisfactorily demonstrate in blood smears the lipid nature of the vacuoles by using formalin vapor as a fixative and staining with Oil red O. Among groups of animals, the numbers of these circulating cells varied with the level of blood cholesterol.

Electron microscopy of the early intimal lesions produced in these rats showed that circulation foam cells appeared to enter the arterial wall by 2 methods: (1) by deposition on the endothelial surface with subsequent incorporation by endothelial overgrowth and (2) by active penetration through the endothelial wall. Thus it seems likely that the circulating macrophage plays an active part in taking up lipid and depositing it in the aortic wall.

Some Social and Cultural Factors Associated with the Incidence of Coronary Heart Disease (P)

S. Leonard Syme, Bethesda, Md., Merton M. Hyman, and Philip E. Enterline, Washington, D. C.

This paper describes the relationship between a number of social and cultural factors and the incidence of coronary heart disease. Factors included are occupation and occupational change, rural-urban residence, physical activity, nativity, and geographical mobility. These factors were found to be most strikingly related to the incidence of coronary heart disease when considered in certain combinations. Men of urban American background, for example, who work in white-collar jobs and who have moved about frequently have, in this sample, a very high incidence of coronary disease. This increased risk is raised even higher when data on fat consumption, smoking, obesity, blood pressure, and parental medical history are superimposed upon the social and cultural data. Thus, intake of dietary fat, by itself, was not found to be related to the incidence of coronary disease. However, when geographically mobile, urban Americans in this sample ingest high quantities of dietary fat, their coronary disease incidence is dramatically elevated. This study is based on data from all white males, aged 35 and over, with new or recurring manifestations of coronary heart disease which developed during 1 year in a 6-county area of North Dakota (203 cases). An age-, sex-, and race-matched control group of 406 subjects, representing the population from which the coronary cases developed, was selected at random from an areal probability sample of all white males, aged 35 and over, living in the 6-county area.

Chemical Analysis of Coronary Atheromas by Infra-red Spectrophotometry

G. Douglas Talbott, James Funkhouser, and James Thompson, Dayton, Ohio

Fifty human hearts had their circumflex and left descending coronary arteries removed, photographed and graded as to luminal obstruction. Two representative specimens from the left descending and circumflex artery were removed and the media and adventitia grossly dissected. Parasaggital sections were obtained on either side of the 2 test specimens and stained with hematoxylin and eosin. The pathologist made a sketch of the degree of microscopic obstruction of the parasaggital sections to correlate with the biochemical assays. Intimal specimens and deposits were then subjected to infra-red spectrophotometry for lipid, inorganic and protein analysis. The findings were correlated with the clinical abstract of each case. Specimen size was of critical importance as previous publications have dealt with 30 to 40 mg. specimens. The specimens in this case were 3 to 4 mg. weight. Lipid percentages were lower in obstructive coronary artery disease than had generally been supposed. The lipid percentage was in the 30 to 40 per cent range in the less severely plaqued arterial segments, whereas a range of 4 to 10 per cent of total lipid was more common in the severely plaqued segments. An inorganic portion showed great variation, and appeared to correlate with the amount of calcification as identified by histologic stain and predicted by the pathologic drawings. The inorganic composition was higher in the grossly obstructed lesion and appeared to be a complex apatite with a probable structure of $Ca_n\ K_n\ Cl_n\ (PO_4)_n\ CO_3$. Lipids and proteins present in the deposits appeared to represent by infra-red spectrophotometry varying mixtures of their classes.

Man's Meager Capacity to Compensate for Dietary (Exogenous) Cholesterol (P)

C. Bruce Taylor, Pacita Manalo-Estrella, Dorothy Patton, and George E. Cox, Evanston, Ill.

Further studies of the sources of plasma cholesterol confirm that most healthy adult humans can obtain only about one-fourth to one-third of their plasma cholesterol from their diet if they ingest about 1 Gm. or more of cholesterol per day. Using dried egg yolk as a medium for feeding cholesterol, 5 groups of subjects ingested (twice daily) constant known doses of 4-C^{14}-labelled cholesterol in egg yolk for 8 weeks or longer (some for 5 months), with radioassay of weekly plasma cholesterol samples. Plasma cholesterol specific radioactivity (counts per minute per mg. cholesterol) progressively increases towards some maximum value that usually is about one-fourth to one-third that of the dietary cholesterol. Using cholesterol-free or cholesterol-low basal diets, supplemented with 2 egg yolks per day containing known quantities of cholesterol, the following approximate levels of daily cholesterol intake have been used: 0.5 (Gm. per day), 0.8, 1.4, 2.4, 4.4, and 10.4. The plasma cholesterol radioactivity curves of the 1.4, 2.4 and 10.4 Gm. per day subjects reach a maximum in 3 to 5 weeks and appear to level off at a constant plateau value thereafter. For the 0.5 and 0.8 Gm. per day subjects, the uptake curves are considerably slower and more erratic. Doses of 0.5 Gm. cholesterol per day supply nearly as large a proportion of plasma cholesterol as do higher dosages; even this may be enough to "saturate" the cholesterol absorption pathway of the average person. Related considerations indicate that the maximum amount of dietary cholesterol that man can compensate for is less than the maximum amount he can absorb.

Behavior and Fate of Injected Plasma Lipids in Corneal Connective Tissues (P)

Levin L. Waters, New Haven, Conn.

Elucidation of the role of diet and of serum lipids in the genesis of arteriosclerosis is a central problem in the pathology of this important condition. The living animal cornea is being used as a pathogenetic model to investigate this relationship. Corneas of rabbits have been injected with 0.1 to 0.01 ml. of plasma, serum, or a pertinent plasma fraction from animals on low-fat diets or on cholesterol-rich diets. Series of rabbits' corneas have been studied after injection with fasting or postprandial samples of human plasma or serum. The following observations have been made: serum lipomicrons and low-density lipoproteins remain in the cornea in proportion to their concentration in the injected plasma or fraction, after fluid and other proteins have disappeared. Lipomicrons, except in the largest concentrations, elicit little or no connective-tissue response. Lipids derived from serum lipoproteins of animal or human source become concentrated in interstitial connective-tissue spaces, lead to damage of connective-tissue elements, and elicit prompt fibroblastic and lipophagocytic reactions. Light-scattering serum lipoproteins of certain low-density classes are active initiators of these processes. Higher density classes remain in the cornea after injection, but are proportionately less active in eliciting connective-tissue responses. However, combined with freshly homogenized aortic connective tissue or with fibrin, the higher density serum lipoproteins, in concentrations obtaining in normal human serum, remain in the cornea after injection and lead to characteristic fatty, foam-cellular tissue reactions.

Influence of Triparanol on Blood Lipids, Yolk Cholesterol and Atherogenesis of Egg-Laying Pullets

Harry Y. C. Wong, Frances M. Farrow, Rose Y. Shim, and Frank B. Johnson, Washington, D.C.

Triparanol at specific dose levels of 12.5 and 25.0 mg./Kg. of body weight of 10-week-old cockerels, either on plain mash or an "atherogenic" regimen, did not alter the blood cholesterol or phospholipid levels of either group after 10 weeks of treatment. In fact, it seems that triparanol enhanced aortic atherogenesis in birds on plain mash diets. The atherogenic diet consisted of 2 per cent cholesterol plus 5 per cent cottonseed oil by weight added to plain mash. The present study on egg-laying pullets was undertaken to observe the effects of triparanol on the blood and egg-yolk cholesterol and phospholipids. Four groups of 31-week-old White Leghorn egg-laying pullets were used as follows: (1) controls receiving olive-oil injections; (2) groups 2, 3, and 4 treated with 50, 75 and 100 mg. of triparanol per Kg. of body weight respectively in olive oil. After 2 weeks of administration of this drug, all triparanol-treated pullets ceased laying. Upon withdrawal of triparanol, blood cholesterol and phospholipid levels increased approximately 3 times the normal values observed. The peak was reached at the end of the fourth week following cessation of injections. Blood cholesterol and phospholipids gradually returned to control levels during the following 4 weeks. Triparanol did not have a hypocholesterolemic influence on egg-laying pullets. The fact that both blood cholesterol and phospholipid levels increased dramatically when the drug was withdrawn strongly suggests further study regarding rate and perhaps method of withdrawal. Currently, we are completing the study on the effect of triparanol on the aorta and coronary arteries of these pullets.

Evaluation of Histochemical and Histologic Methods Used in Cardiovascular Research

Frederick T. Zugibe, and M. L. Fink, Pittsburgh, Pa.

Many of the conflicting reports in the literature concerning histochemical and histologic studies are due to inadequate technics. A series of histochemical and histologic methods commonly used in atherosclerosis research were critically studied to determine the specificity, mode of action, method of choice and contraindications. These included methods for lipids, acid mucopolysaccharides, neutral mucopolysaccharides, collagen, glycogen, as well as fixatives, embedding technics and hydrolytic enzyme technics. The results of this study are as follows: Carbowax 400 is the lipid stain solvent of choice, having distinct advantages over other solvents. Suitable controls on adjacent sections with lipid solvents are necessary to eliminate other substances that take up the stain (ceroid, Cioccio's lipoids, unsaturated fats, etc.). The most specific technic for demonstrating acid mucopolysaccharides in arteries is alcian blue at a pH of 2.2. Mowry's modification of alcian blue (pH 2.5) also stains sialic acid (pK 0.5) which is also present in aortas. The other acid mucopolysaccharide technics have been considered. The periodic acid-Schiff method must be interpreted with caution because positive staining following diatase treatment may be contributed to by various substances present in the tissue (unsaturated lipids, traces of formaldehyde, sialomucins, keratosulfate, etc.) other than neutral mucopolysaccharides. The use of appropriate controls and blocking agents has been considered. Chlorantine fast red gave less residual staining after purified collagenase treatment than the commonly used collagen stains (Massons, Amidigo, Schwarz, naphthol blue black, Van Giesons, Heidenhains, Mallory's PTAH). Advantages of the carbowax embedding technic over frozen sectioning for demonstrating lipids, the quaternary ammonium technics for acid mucopolysaccharide precipitation and the utilization of hydrolytic enzymes as histochemical reagents have been evaluated.

Histochemical Studies of the Coronary Arteries and Aortas of the Minipig

Frederick T. Zugibe, and M. L. Fink, Pittsburgh, Pa.

A histochemical study of coronary arteries and aortas from 12 9-month-old minipigs has been made utilizing new histochemical technics developed in our laboratory. Notable among these technics is a new method for demonstrating and identifying the individual acid mucopolysaccharides in tissue sections as well as a method for demonstrating acid mucopolysaccharides and lipids on the same tissue section. Tissue samples were taken from both atheromatous and adjacent grossly normal areas in the transverse aortic arch, thoracic aorta, abdominal aorta, right coronary artery, and the anterior descending and circumflex branches of the left coronary artery. A preliminary report of our observations is as follows: There is no relation between acid mucopolysaccharides (AMP) and lipid in respect to staining intensity and/or distribution. Minimal-to-moderate intimal lipid accumulations were noted in all the atheromatous areas, in the coronary intimas of all the pigs, in the majority of coronary medias, and in the majority of the grossly normal aortic intimas. Lipid was never found within the internal elastic membrane, as was previously reported in human aortas, cerebral arteries and coronary arteries. Fragmentation, fraying and reduplication of the internal elastic membrane were present in both the grossly normal and atheromatous areas in all the coronary artery sections. In the aorta sections, all the atheromatous areas and the majority of the normal areas had varying degrees of fragmentation and reduplication, most severe in the arch area and less severe in the abdominal areas. There was an accumulation of AMP associated with these elastic changes. This AMP was comprised of chondroitin sulfate A and/or C and chondroitin sulfate B, with the ratio of B to A and/or C increasing with severity of elastic changes. There was a close relationship between collagen fibers and the AMP, suggesting a reinforcement mechanism to strengthen the arterial wall. A comparison of these findings with our previously reported findings in human aortas, coronary arteries and cerebral arteries has been made. The significance of these findings has been considered.

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